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Your observing optician offers this suggestion to benefit the ophthalmologist, the patient, and incidentally, the optician.

"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

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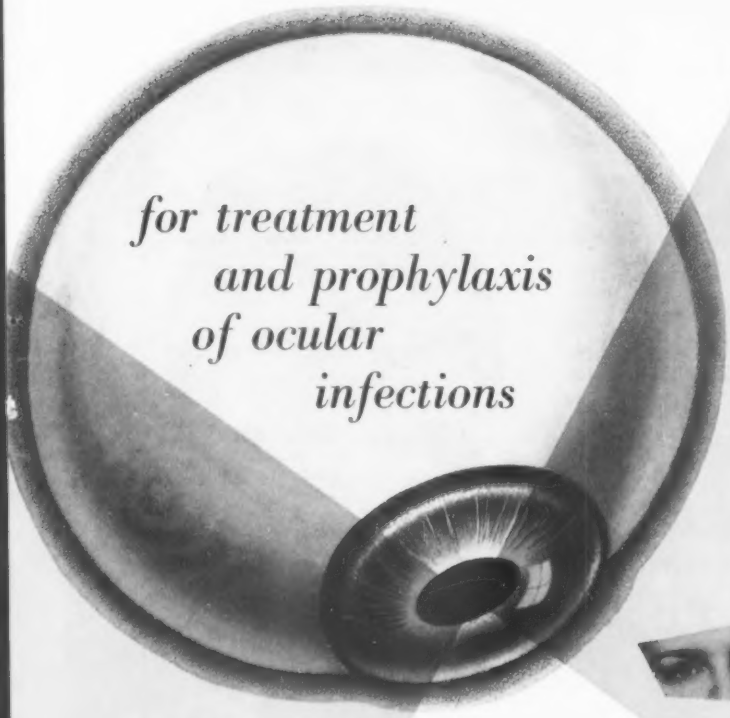

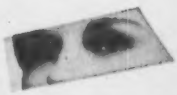

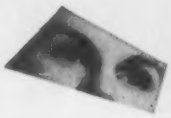

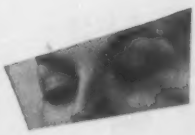

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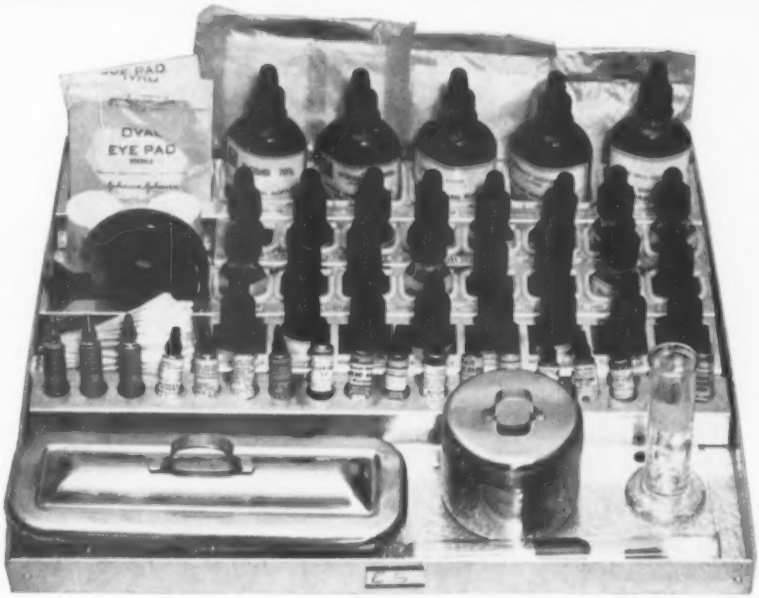

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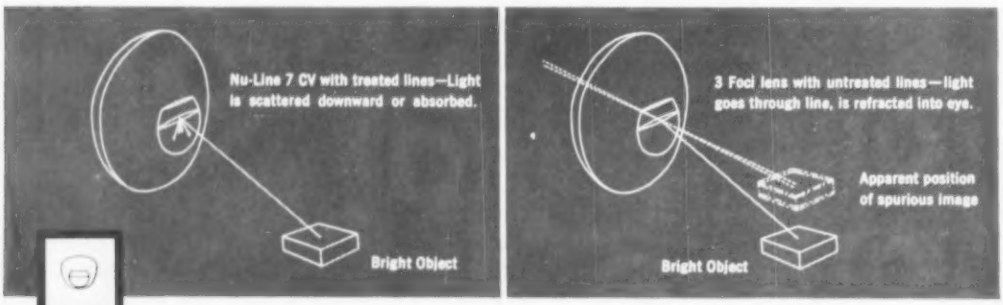
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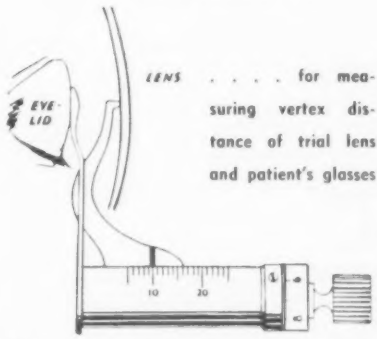

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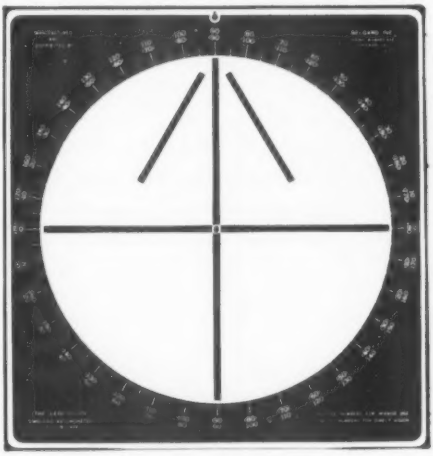

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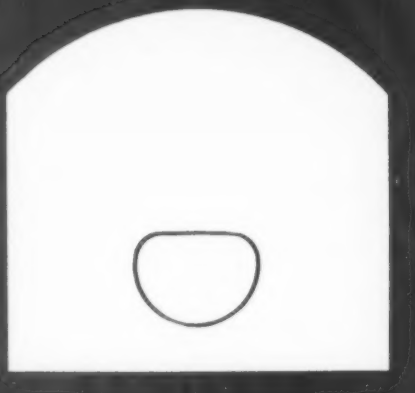

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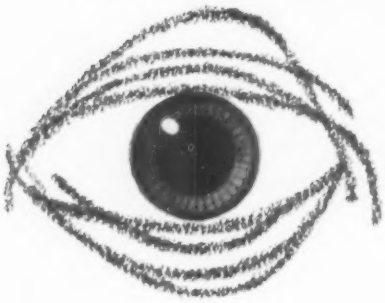

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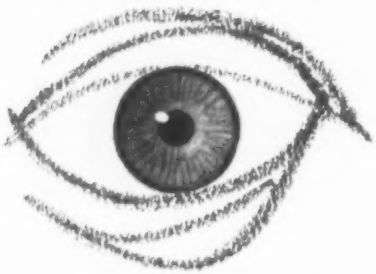

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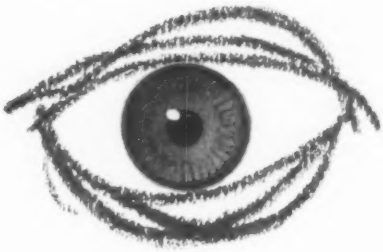

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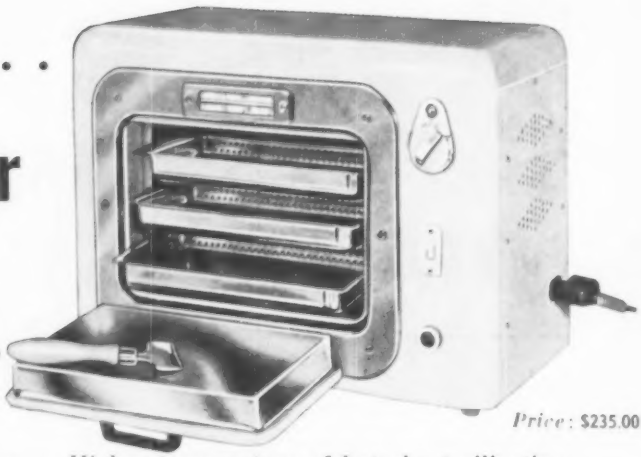

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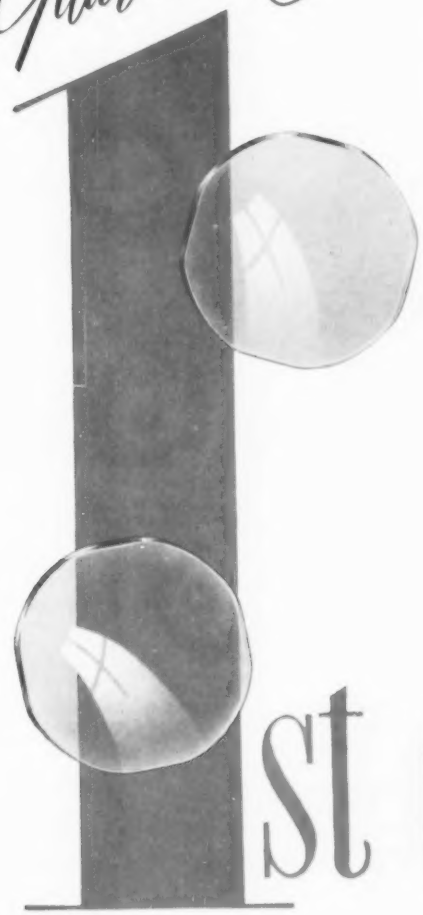

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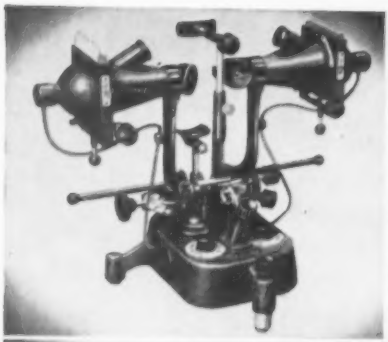

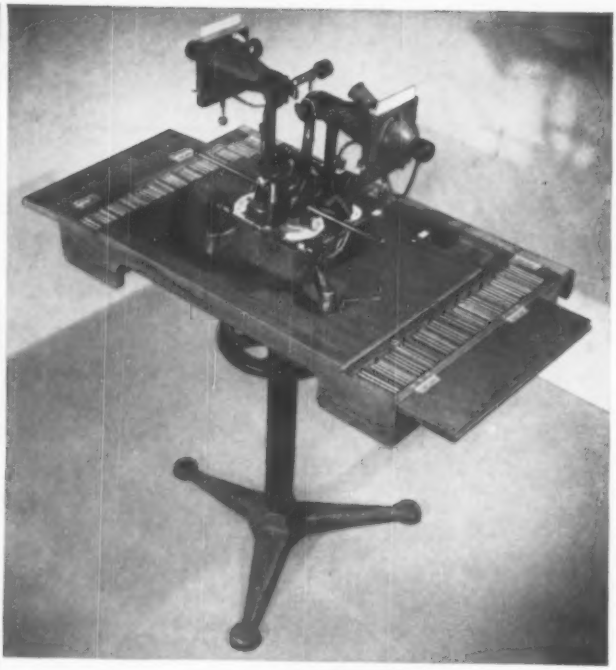

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DIAMOX (ACETAZOLEAMIDE) IN TREATMENT OF GLAUCOMA

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AND
ROBERT R. TROTTER, M.D.
BOSTON

A COROLLARY of Friedenwald's concept of bicarbonate secretion in the formation of aqueous humor is that inhibition of the enzyme carbonic anhydrase might be expected to decrease the rate of secretion and lower the intraocular pressure. Thus it was not surprising when the carbonic anhydrase inhibitor Diamox * (acetazoleamide) became available and was found safe for human beings, that several investigators should have given it a trial in glaucoma simultaneously and independently. Some of these results have been published,[1] and many others may be expected in the near future. The following is a report of our initial experience.†

Preliminary trials of Diamox in rabbits produced definite lowering of intraocular pressure when 10 to 100 mg. per kilogram was injected intravenously. However, no significant effect on intraocular pressure was obtained when a saturated solution of Diamox was dropped repeatedly on the cornea or injected subconjunctivally.

CLINICAL INVESTIGATION

Clinical trials, in both normal and glaucomatous patients, were carried out by administering the drug orally except in cases in which vomiting accompanied acute glaucoma and necessitated intravenous administration. Frequent tonometric and occasional tonographic measurements were made, and all eyes were examined gonioscopically. In all cases comparison of intraocular pressure before and after administration of Diamox was the prime interest. Toxic effects were also looked for.

Results in Patients.—The effect of Diamox was investigated in 40 patients, of whom 8 were entirely normal and 32 had various types of glaucoma, involving 50 eyes. The dosage of Diamox ranged from 125 to 500 mg. given orally every 12 hours, and in a few cases a single injection of 250 to 500 mg. was given intravenously.

Without regard to the type of glaucoma, the general effect of Diamox on the intraocular pressure is summarized in the Chart for the 53 eyes in which the effect

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and Massachusetts Eye and Ear Infirmary.

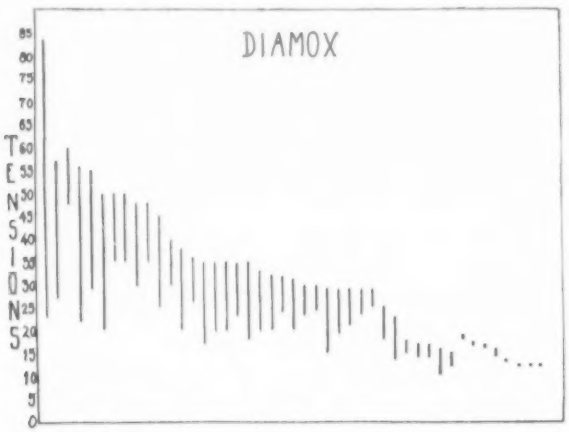
This investigation was supported by Research Grant B-218 from the Institute of Neurological Diseases and Blindness of the National Institutes of Health, United States Public Health Service.

* Diamox (brand of acetazoleamide) was supplied gratis by Lederle Laboratories for these investigations, through the interest of Dr. James Gallagher.

† Presented at the meeting of the New England Ophthalmological Society on Feb. 17, 1954.

could be most clearly attributed to the action of the drug. In this Chart the data have been lined up graphically with the top of each solid line, indicating the height of the intraocular pressure before administration of Diamox, and the lower end of the line, showing in each instance to what level the pressure dropped. Each of the eight short lines at the right hand of the Chart represents a pair of normal eyes, but all other lines represent single glaucomatous eyes. It appears from this graph that the effect of Diamox is somewhat in proportion to the initial pressure, and that commonly the pressure is lowered by about a third. However, a number of exceptions to this generalization are obvious.

Normal Eyes.—Diamox at the dose employed clinically had little effect on normal human eyes. In these eyes the tensions were all less than 20 mm. (electronic Schiøtz) without treatment, and no change in tension was found in eight of the eyes and only a 1 to 2 mm. decrease in the other eight when Diamox was admin-



The series of vertical lines represents the decreases of tension (in millimeters, Electronic Schiøtz) which were produced by Diamox in a series of patients' eyes. The top of the line indicates the tension before, and the bottom of the line the tension after, medication in each case.

istered orally at the rate of 250 mg. twice a day for one to five days. This response was only slightly less than that produced by Diamox in glaucomatous eyes which were at comparable initial pressures under the influence of standard miotic drugs. The same dose of Diamox produced only a 3 mm. decrease in four out of five of these eyes. (The dose employed in these clinical observations was smaller on a body weight basis than that which effectively lowered the pressure in normal rabbit eyes.)

Acute Angle-Closure (Narrow-Angle) Glaucoma.—In the two cases of this type Diamox produced a larger effect than in other conditions. (Subsequent experiences have been similar.) In one case the tension was 83 mm. despite intensive treatment with standard miotic drugs, and gonioscopy showed the angle to be completely closed. Administration of pilocarpine was continued, and intravenous injection of 500 mg. of Diamox in 10 ml. of water was given. The tension was lowered to 77 mm. in

30 minutes, to 63 mm. in 90 minutes, and to 37 mm. in 4 hours after injection, but at 7 hours the tension was again rising. After additional administration of 500 mg. of Diamox by mouth the tension dropped to 23 mm. in six hours, and by repetition of the medication it was kept there until operation the next day. When the tension was lowered by Diamox, gonioscopy showed the angle to have opened in half the circumference. In the second case the tension was only 55 mm. but could be lowered no further with miotics; the pupil was semidilated and unresponsive, and the angle was seen to be closed. After 250 mg. of Diamox was given intravenously, and then orally every six hours, the tension was reduced to 22 mm. in 18 hours; the pupil became constricted and the angle opened, although it was very narrow. Iridectomy was performed without appreciable delay in re-formation of the anterior chamber in either case. The extent of pressure reduction by Diamox in reversible angle-closure glaucoma may be explained by a dual effect in this condition. At the high initial pressure the iris sphincter is probably paralyzed, as described by Tyner and Scheie,[2] but with some lowering of the pressure by Diamox the sphincter regains its responsiveness and aids in withdrawing the iris from contact with the filtration meshwork in the angle. On this basis, it appears advisable to continue administration of miotic drugs while giving Diamox, as was done in the cases described here.

Open-Angle (Wide-Angle or Chronic Simple) Glaucoma.—Of 23 eyes with the primary condition and 8 eyes with glaucoma secondary to capsular exfoliation and pigment accumulation in the filtration meshwork, a beneficial effect was obtained from Diamox in all but 1. In most patients on a dose of 250 mg. orally every 12 hours the tension was lowered by about a third. In a few cases 250 mg. was required three to four times a day to obtain the same effect. No local treatment was applied to several of the eyes, but the majority were maintained on constant standard topical medication before and during the trial of Diamox. It appeared from comparison of these eyes that the pressure-lowering effect of Diamox was essentially independent of and additive to the effects of the standard miotic drugs and epinephrine. No interference was observed. In 18 of the eyes with open-angle glaucoma which had been inadequately controlled by standard topical medications the pressure was lowered to the normal range by supplementary treatment with Diamox. The ultimate duration of this improved control has not be established, but most eyes were doing well after four weeks, and six were satisfactorily controlled at 9 to 11 weeks. No difference in effectiveness of Diamox was found in eyes which were aphakic.

Acute Glaucoma Secondary to Iridocyclitis.—Lowering of the pressure was obtained in two cases of this type by means of oral Diamox therapy when standard local treatment was inadequate. The iridocyclitis subsided during treatment in both cases.

Glaucoma Due to Extensive Peripheral Anterior Synechias.—In this condition, resulting from previous attacks of uveitis, from angle-closure (narrow-angle) glaucoma, or from flat chamber complicating intraocular operation, the results of treatment with Diamox have been relatively poor. In 11 eyes with extensive peripheral anterior synechias in which control of tension with standard topical medications was inadequate, addition of oral Diamox therapy did not normalize the tensions. Only partial relief was gained with Diamox in doses which would be feasible for constant administration.

Side-Effects.—Some side-effects from the administration of Diamox have been noticed in most cases but have not been serious. No ocular side-effects or toxic manifestations have yet been noted. The systemic side-effects are the same as have been reported in other studies. These systemic side-effects impose some limitations on the usefulness of Diamox, particularly for prolonged administration. Although we have observed no unpleasant reactions from initial doses of 500 mg. given either orally or intravenously, almost all our patients who have received 250 mg. two to four times a day for several days have been discomforted by "pins and needles" paresthesias, particularly in the face, hands, or feet. This dose and frequency of administration are both greater than are recommended in treatment of generalized edema from cardiac decompensation. Such frequent administration makes no allowance for a diurnal acid-base balance "recovery" period. Occasional trials of cessation of treatment for "recovery" have revealed no benefit to the management of glaucoma. In fact, for adequate effect in glaucoma it has usually been found necessary to employ Diamox to about the extent to which the patient can tolerate its side-effects. Oral administration at 12-hour intervals has provided satisfactory control of pressure in most cases, but less frequent use has not. Administration at six-hour intervals may have some advantage. When Diamox has been discontinued, all side-effects have disappeared within a day, suggesting that they represent functional rather than organic disturbances.

The mode of action of Diamox in lowering the intraocular pressure is not established, but tonographic measurements have indicated that, with the exception of the cases of reversible angle-closure glaucoma, the pressure is usually reduced without commensurate improvement in facility of aqueous outflow. This is taken to indicate that the pressure in these cases has been reduced by a decrease in rate of formation of aqueous humor. Clinical evidence also supports this interpretation in cases of glaucoma from complete closure of the angle, in which Diamox may produce a considerable lowering of the pressure. Fortunately, the decrease in rate of aqueous production in patients has not been enough to delay re-formation of the anterior chamber in the few instances in which iridectomy has been performed while the drug was being administered.

SUMMARY

Diamox, a carbonic anhydrase inhibitor (acetazoleamide), is a safe and helpful drug in the treatment of certain types of glaucoma.

Its value seems most definite as a supplement to the standard miotic drugs in the relief of acute angle-closure glaucoma. Administered orally or intravenously, Diamox is effective in lowering the intraocular pressure so that the pupil may constrict to open the angle and prepare the eye for iridectomy.

In attacks of glaucoma secondary to iridocyclitis Diamox also appears to be helpful as a supplement to the standard local medications.

In long-term treatment of chronic open-angle glaucoma, Diamox is still in a trial period. In most cases an initial lowering of intraocular pressure by about one-third is produced by administering 250 mg. of this drug two to four times a day. In some cases this effect has been maintained for only a week or two, while in

others there has been no loss of effect within two and a half months. The effect of Diamox is additive to that of the standard miotic drugs and epinephrine in chronic open-angle glaucoma, and it appears that systemic treatment with Diamox should be regarded as a potential supplement to the standard topical medications.

In severe glaucoma due to peripheral anterior synechias and in hemorrhagic glaucoma only slightly helpful or transient lowering of the pressure has been obtained so far in our experience.

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RELATION OF TONOGRAPHY TO PHASIC VARIATIONS OF INTRAOCULAR PRESSURE

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NEW YORK

THERE ARE many reports in the literature concerning the spontaneous diurnal changes in the intraocular pressure of both normal and glaucomatous eyes. In the last few years the most notable studies on this subject took place at the Institute of Ophthalmology in London * and were reviewed in an excellent paper by Sir Stewart Duke-Elder.[3] The workers here studied both the chronic simple and the congestive type of glaucomatous eyes and noted marked variations in the intraocular pressure over 24-hour periods. Since their studies appeared, Grant † has published the results of his work on aqueous humor dynamics, by a method which is commonly known as the aqueous outflow test, or tonography. Since the cause of the spontaneous changes in the intraocular pressure is not well understood, it was thought that a correlation of Grant's † aqueous outflow test with the diurnal intraocular pressure changes might shed some light on the mechanics of the aqueous humor dynamics. Therefore, in an attempt at further understanding of the mechanism of primary glaucoma, the following study was undertaken.

MATERIALS AND METHODS

The majority of the patients for the present study were taken from the Glaucoma Clinic of the Institute of Ophthalmology in London; some of them were from the Glaucoma Clinic of the Institute of Ophthalmology of the Presbyterian Hospital in New York. For the purpose of the present discussion chronic simple, or wide-angle, glaucoma is defined as a disease consisting of raised intraocular pressure with field changes and cupping of the optic disc; the anterior chamber angle is open at all times, even during the increase in the intraocular pressure. Congestive, or narrow-angle, glaucoma is characterized by a narrow chamber angle, full peripheral and central fields of vision, and absence of cupping of the optic disc in the early stages of the disease, together with a closure of the angle when the intraocular pressure rises. The spontaneous changes in the intraocular pressure during the course of the day are usually measured over a 24-hour period, thus requiring hospitalization of the patient; the intraocular pressure is noted every two or three hours. However, with tonography this procedure appeared to be impractical, for several reasons. In the first place, it would have been ill-advised to subject an eye to tonography every two or three hours over a course of 24 hours because of possible damage to the corneal epithelium. Therefore, it was arbitrarily decided to do four or five aqueous outflow tests on each eye during the course of the day, the first test being performed between 9:00 and 10:00 in the morning, the second test usually about noon, the third test after lunch, the fourth

This study was supported by the Sloan Glaucoma Fund.

From the Glaucoma Clinic, Institute of Ophthalmology, London, Director of Research, Sir Stewart Duke-Elder; and from the Institute of Ophthalmology of the Presbyterian Hospital, New York.

* References 1 and 2.

† References 4 to 6.

test about 4:00 in the afternoon, and, if necessary, the fifth, and final, test about 5:30 or 6:00 in the afternoon. It was considered that four or five tonographic tests over a single day would probably not damage the corneal epithelium. Several of these eyes were stained at the end of the day, but none of them showed defects in the corneal epithelium. Nevertheless, many patients complained at the end of the day of mild discomfort in the eye, and it was considered that four or five tonographic tests was probably about the limit that the patient would tolerate in the course of a single day. Also, with the procedure outlined above, the necessity for hospitalization was eliminated, thereby allowing the patients to be treated on an ambulatory basis. Even over this eight-hour period during the course of the working hours of the day, significant changes were obtained, and therefore the full 24-hour measurements were not considered necessary.

The tension was taken with the electronic tonometer,‡ and the aqueous outflow test was carried out according to the method of Grant, employing the four-minute, or so-called abbreviated, test. A word of caution should be expressed at this point concerning the limit of accuracy of tonography. Friedenwald, in a discussion of Grant's paper, was the first to point out the large variation of the results with this new test from one eye to the next, due to differences in scleral rigidity, corneal curvatures, etc. This applies both to the facility of aqueous outflow and to the total rate of flow. Therefore, one should not attach undue importance to the absolute values obtained by this test when comparing one eye with another or when comparing the readings with the previously established normal values. When tonography is repeated at intervals on the same eye, however, the relative values obtained in this manner are not seriously affected by the above-mentioned factors, and thus the test will reveal changes in aqueous humor dynamics. For the purposes of the present investigation, these relative values obtained by repeated tonography on the same eye will be considered primarily.

Each of these patients had a well-documented history in the Glaucoma Clinic and were followed anywhere from two months to five years. Most of them had primary glaucoma, but a few normal subjects were included in this series for reasons of comparison. Their examination included visual fields, gonioscopy, and provocative tests, besides the carefully noted history and physical examination of the eye.

The patients for the water-drinking test [7] were chosen from a group with chronic simple, wide-angle glaucoma who had not been operated on and who had had positive water-drinking tests in the past, thus assuring a considerable rise in intraocular pressure following the test, which was desired for the purposes of the present examination. The water-drinking test was performed in the morning on a fasting stomach, the patient being allowed no breakfast, only a cup of tea early on arising. Before the water-drinking test was performed, the intraocular pressure was measured several times prior to the test in order to rule out a rising or descending phase of the intraocular pressure. If, preceding the test, there were marked changes in the intraocular pressure, the test was postponed. By this means the possible effect of a sudden rising or descending phase of intraocular pressure on the outcome of the water-drinking test was considered to be eliminated. One liter of water was then drunk by the patients within a four-minute period. Tonography was performed preceding and 30 minutes after the ingestion of water. This routine was established arbitrarily, since the height of the elevation of the intraocular pressure occurs approximately 30 minutes after drinking the water. Repetition of the tonography more frequently would be inadvisable because of the time required for recovery following each aqueous outflow test.

Previous experience with tonography showed that the aqueous outflow test has a pressure-lowering effect on the fellow eye in most instances. For example, if the intraocular pressure is measured in the left eye before and immediately after doing the aqueous outflow test on the right eye, a small, but appreciable, drop in the intraocular pressure can be measured in the left eye. Thus, performing the test immediately on the second eye as soon as one is finished with the first eye might not yield the correct information. Therefore, to prevent this pressure-lowering effect from interfering with the test, four or five minutes was allowed to elapse between the tonographic tests on the two eyes. This pressure-lowering effect on the fellow eye was noticed also by Knighton § and Blaxter,‖ but its cause is unknown.

‡ Manufactured by V. Mueller and Company, Chicago.

§ Knighton, W. S.: Personal communication to the author.

‖ Blaxter, P.: Personal communication to the author.

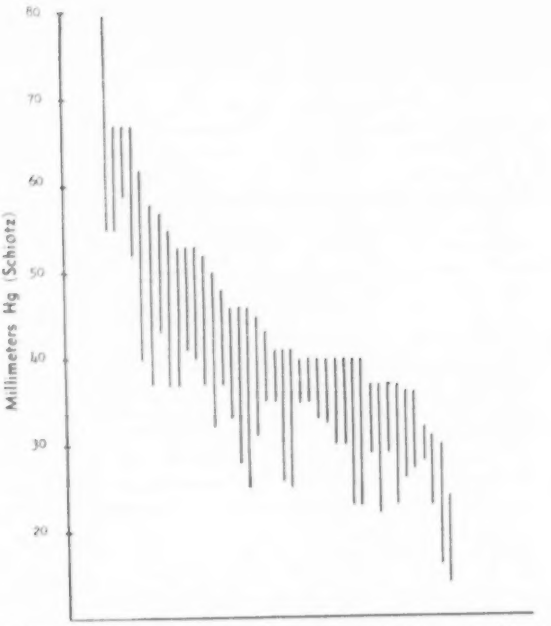

Chart 1.—Diurnal variation in intraocular pressure in 40 eyes with chronic simple, wide-angle glaucoma that had not been operated on and had had no medication for 36 hours preceding the test. Each vertical line represents the highest and the lowest tension recorded during one day in an individual eye.

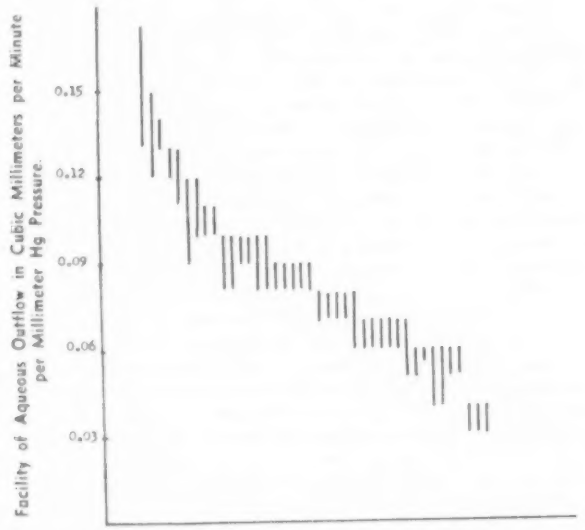

Chart 2.—Diurnal variation in the facility of aqueous outflow in 40 eyes with chronic simple, wide-angle glaucoma that had not been operated on and had had no medication for 36 hours preceding the test. Each vertical line represents the highest and the lowest facility of outflow measurement recorded during one day in an individual eye.

RESULTS

Normal Eyes.—A few control experiments were performed on normal eyes, and it soon became apparent that during the course of the day there were only minor variations in the intraocular pressure and that the aqueous outflow remained approximately the same, staying well within the normal range.

Chronic Simple, or Wide-Angle, Glaucoma.—Forty eyes of this type that had had no previous operation and that had had no medication for at least 36 hours preceding the test were studied. Chart 1 shows the changes in the tension that took place in the eyes over the course of the day, demonstrating a considerable variation of the intraocular pressure. As a rule, most of these eyes showed a double-variation type of curve; that is, the intraocular pressure was highest in the morning hours, had

TABLE 1.—*Diurnal Variations in Facility of Aqueous Outflow* and in Intraocular Pressure in a Patient's Eyes with Early Chronic Simple, Wide-Angle Glaucoma, Without Surgical or Medical Treatment*

	O.D.		O.S.	
Time	C	I.O.P., Mm. Hg	C	I.O.P., Mm. Hg
9:30 a. m.	0.07	46	0.06	58
12 N.	0.07	37	0.07	43
2:10 p. m.	0.08	33	0.07	37
4:00 p. m.	0.07	29	0.07	30
5:15 p. m.	0.07	32	0.08	39

* C indicates cubic millimeters per minute per millimeter Hg pressure.

TABLE 2.—*Diurnal Variations in Facility of Aqueous Outflow* and in Intraocular Pressure of an Eye (Right) with Long-Standing and Far-Advanced Chronic Simple Wide-Angle Glaucoma, Not Operated on and Without Miotics for Thirty-Six Hours Prior to this Test*

Time	C	I.O.P., Mm. Hg
9:50 a. m.	0.04	72
11:50 a. m.	0.03	80
2:10 p. m.	0.03	55
4:40 p. m.	0.04	77

* C indicates cubic millimeters per minute per millimeter Hg pressure.

a tendency to fall after lunch, and rose again around 4 p. m. This finding substantiates the results of Langley. Chart 2 shows the variation in the facility of aqueous outflow in these same eyes during the course of the day, demonstrating that the facility of aqueous outflow, as measured by tonography, did not change considerably, while at the same time the intraocular pressure showed marked variations. Table 1 illustrates a typical case. This patient had early chronic simple glaucoma that had not been operated on and that had had no medication for 48 hours prior to this examination. The facility of aqueous outflow changed only to a minimal extent (the variation being within the limits of the experimental error of the test itself) during the course of the day, while simultaneously the intraocular pressure dropped considerably. Table 2 demonstrates another typical case of chronic simple glaucoma. However, in this case the eye was in a late stage, with deep cupping and marked field loss, and the base pressure was considerably elevated. This eye also demonstrated spontaneous diurnal changes in intraocular pressure, while at the same time

the facility of the aqueous outflow again remained almost stationary. The total rate of flow of aqueous was also calculated for each tonographic test, but the results thus obtained were variable and did not contribute a great deal toward the outcome of the experiment; therefore, the values for the total rate of flow are not reported in this part of the study. In the water-drinking experiment, on the other hand, as will be shown below, the calculated values for the total rate of flow are included in the results because there they seemed significant and contributed to a better understanding of the problem.

The experiment was also performed on 15 eyes with chronic simple glaucoma that had had some sort of antiglaucoma operation in the past or were receiving medication. Table 3 illustrates a typical case. It shows the results obtained on a patient whose right eye was controlled with miotic medication and whose left eye had had a corneoscleral trephination several years prior to this examination. In both eyes the intraocular pressure stayed approximately within normal limits during the course of the day, and the facility of aqueous outflow showed some variation in the normal range. However, while the variation in the intraocular pressure was only

TABLE 3.—*Diurnal Variations in Facility of Aqueous Outflow* and in Intraocular Pressure of a Patient's Eyes with Chronic Simple, Wide-Angle Glaucoma†*

	O.D.		O.S.	
Time	C	I.O.P., Mm. Hg	C	I.O.P., Mm. Hg
10:00 a. m.	0.25	25	0.20	26
12 N.	0.16	28	0.22	23
2:00 p. m.	0.26	24	0.26	22
4:00 p. m.	0.18	26	0.21	22
5:30 p. m.	0.33	22	....	..

* C indicates cubic millimeters per minute per millimeter Hg pressure.

† The right eye was not operated on and received 1% physostigmine salicylate three times a day. The left eye had had a corneoscleral trephination five years ago, draining a conjunctival bleb at 12 o'clock; no medication.

minimal in these eyes, the facility of aqueous outflow did vary somewhat more than is usually found in a normal eye, but always within the normal range. This observation was particularly noticeable in the eye under miotic medication, the eye being treated with 0.25% physostigmine salicylate three times a day. The apparent changes in the facility of aqueous outflow in this eye might have been due to the uneven distribution of the medication during the day, since it is known that miotics will considerably improve the facility of aqueous outflow in eyes with this type of glaucoma.

Water-Drinking Test.—Charts 3 and 4 show the effect of the water-drinking test on the intraocular pressure and on the facility of aqueous outflow in 22 eyes with chronic simple, wide-angle glaucoma that had not been operated on and that were without miotics for at least 36 hours prior to examination. These eyes all showed a positive water-drinking test, the pressure increasing considerably after the ingestion of 1 liter of water. However, at the same time, the facility of aqueous outflow as measured by tonography changed only minimally. Tables 4 and 5 illustrate two typical cases: Table 4 shows a patient with early chronic simple glaucoma, minimal field defect, and small cupping of the optic discs. The intraocular pressure was within normal range at the beginning of the examination, but it rose to a maximum of 40 mm. Hg; at the same time, however, the facility of aqueous

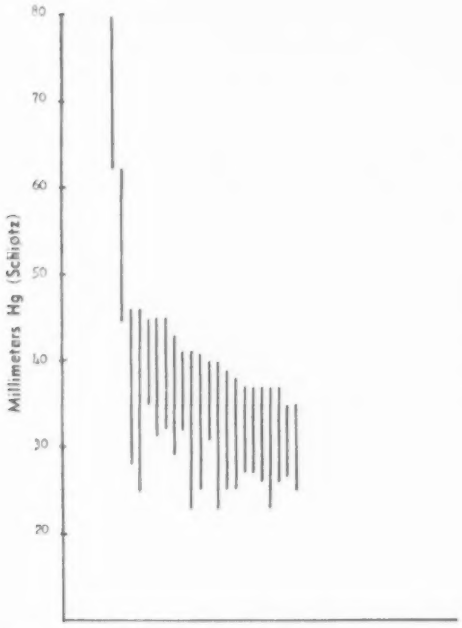

Chart 3.—Effect of water-drinking test (1 liter in four minutes on a fasting stomach) on the intraocular pressure in 22 eyes with chronic simple, wide-angle glaucoma that had not been operated on and had not been treated. Each vertical line represents the change in intraocular pressure from just before to 30 minutes after the test in an individual eye.

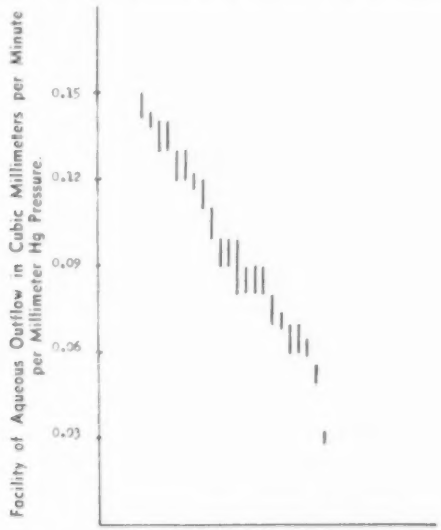

Chart 4.—Effect of water-drinking test (1 liter in four minutes on a fasting stomach) on the facility of aqueous outflow in 22 eyes with chronic simple, wide-angle glaucoma that had not been operated on and that had not received treatment. Each vertical line represents the change in intraocular pressure from just before to 30 minutes after the test in an individual eye.

outflow stayed about the same. A subsequent drop of the intraocular pressure (back to normal levels) followed in the next few hours, but the facility of aqueous outflow did not change appreciably. The rate of aqueous outflow, however, did show changes corresponding to the variations in intraocular pressure; it increased as the intraocular pressure rose, and it dropped back to the pretest level as the intraocular pressure also tended to fall. Concerning the mechanism of the water-drinking test, the majority of workers in this field believe that the sudden hemodilution caused by the water intake lowers the osmotic pressure of the blood, thus enhancing the difference in the osmotic pressures of the blood and of the aqueous humor. This, in turn, would tend to pull more water from the blood into the aqueous, thus increasing temporarily the rate of flow of aqueous humor in the anterior chamber. The present experiment demonstrates that in eyes with untreated chronic simple glaucoma the water-drinking test did increase the rate of flow of aqueous in the anterior chamber. Thus, tonography tends to substantiate the current belief concerning the mechanism

TABLE 4.—*Effect of Water-Drinking Test* on Facility of Aqueous Outflow† on Total Rate of Flow and on Intraocular Pressure in an Eye (Left) with Chronic Simple, Wide-Angle Glaucoma in Its Early Stage Which Had No Surgical or Medical Treatment*

Time	C	K, Cu. Mm. Min.	I.O.P., Mm. Hg
10:00 a. m.	0.09	1.8	23
10:15 a. m.	....	....	24
10:30 a. m.	....	....	23
10:35 a. m.	1 liter of water taken orally in 4 min.		
10:45 a. m.	....	....	37
10:55 a. m.	....	....	38
11:10 a. m.	0.08	3.0	40
11:45 a. m.	....	....	30
12:15 p. m.	....	....	25
1:20 p. m.	0.09	1.8	24

* One liter of water on a fasting stomach.

† C indicates cubic millimeters per minute per millimeter Hg pressure.

of the water-drinking test. Table 5 demonstrates another case of chronic simple glaucoma. In this patient, however, the disease was far advanced, and the intraocular pressure was at a much higher level. In this eye, also, we can note the typical rise in the intraocular pressure following the drinking of 1 liter of water, and, again, there is noted the lack of change in the facility of aqueous outflow, while the rate of aqueous outflow paralleled the variations in intraocular pressure.

Congestive, or Narrow-Angle, Glaucoma.—Forty eyes with congestive, or narrow-angle, glaucoma were also studied. As a general rule, in these eyes the changes in intraocular pressure were reflected simultaneously in the facility of aqueous outflow; i. e., as the intraocular pressure rose, the facility of aqueous outflow correspondingly decreased toward the glaucomatous range, and, conversely, when the intraocular pressure dropped—either spontaneously or under the influence of miotic medication—the facility of aqueous outflow also improved and the coefficient then moved toward the higher, or more normal, range. Table 6 demonstrates such a typical case of congestive glaucoma that was not under miotic medication at the time of examination. The intraocular pressure rose during the course of the day, and,

correspondingly, there was also a decrease in the facility of aqueous outflow; toward the end of the day there was a spontaneous drop in the intraocular pressure, and simultaneously the facility of aqueous outflow improved. Table 7 demonstrates a

TABLE 5.—*Effect of Water-Drinking Test* on Facility of Aqueous Outflow,† on Total Rate of Flow, and on Intraocular Pressure in an Eye (Left) with Far-Advanced, Chronic Simple, Wide-Angle Glaucoma That Had No Medication for Thirty-Six Hours Prior to the Test*

Time	C	K, Cu. Mm./Min.	I.O.P., Mm. Hg
9:50 a. m.	0.03	1.7	55
10:00 a. m.	....	...	57
11:10 a. m.	....	...	56
11:15 a. m.	1 liter of water taken orally in 4 min.		
11:30 a. m.	....	...	65
11:40 a. m.	....	...	72
11:50 a. m.	....	3.2	77
12:00 p. m.	....	...	74
1:00 p. m.	....	...	65
2:00 p. m.	0.04	1.8	52

* One liter of water given on a fasting stomach.
† C indicates cubic millimeters per minute per millimeter Hg pressure.

TABLE 6.—*Diurnal Changes in Facility of Aqueous Outflow* and in Intraocular Pressure in an Eye (Right) with Congestive, Narrow-Angle Glaucoma Untreated Surgically or Medically*

Time	C	I.O.P., Mm. Hg
10:00 a. m.	0.10	46
12:00 N.	0.06	56
2:00 p. m.	0.05	63
3:30 p. m.	0.04	67
5:30 p. m.	0.11	41

* C indicates cubic millimeters per minute per millimeter Hg pressure.

TABLE 7.—*Diurnal Changes in Facility of Aqueous Outflow and in Intraocular Pressure in an Eye (Right) with Congestive, Narrow-Angle Glaucoma Which Had Not Been Operated On and Had Had No Medication for Thirty-Six Hours Prior to the Test*

Time	C*	I.O.P., Mm. Hg
10:00 a. m.	0.20	14
12:00 N.	0.16	22
2:00 p. m.	0.13	22
3:40 p. m.	0.03	63
4:00 p. m.†	Physostigmine, 1%, instilled	
5:00 p. m.	0.31	23

* C indicates cubic millimeters per minute per millimeter Hg pressure.
† Because of the sudden rise in tension in the afternoon, 1 drop of 1% physostigmine salicylate was instilled in the eye at 4 p. m.

similar eye with congestive glaucoma which started out in the morning with normal intraocular pressure, but early in the afternoon suffered a sudden, spontaneous, marked increase in the intraocular pressure, which was reflected in the sudden decrease in the facility of aqueous outflow. Because of this sudden rise in intraocular pressure and the congestive symptoms noticed by the patient—mainly halos and

pain—1% physostigmine was then instilled in the eye; an hour later the intraocular pressure was in the normal range and at the same time the facility of aqueous outflow was much improved and well up toward the normal level. Gonioscopic observations ¶ carried out on these patients showed a tendency to angle closure corresponding to the spontaneous rises in intraocular pressure and an opening up of the angle when the intraocular pressure dropped, either spontaneously or under the influence of the miotic. Such correlation of the appearance of the anterior chamber angle with the intraocular pressure and the facility of aqueous outflow was previously demonstrated and emphasized by Grant.

COMMENT

The most significant observation in this study is the fact that in the chronic simple, wide-angle type of glaucoma when the eye is not under miotic medication, the spontaneous diurnal or artificially induced (water-drinking test) changes in the intraocular pressure are not followed by similar changes in the facility of aqueous outflow as measured by tonography. This appears to be true in the very early stages of this disease, with only low or minimal rises in the intraocular pressure, and it also appears to be the case with far-advanced chronic simple glaucoma, when the intraocular pressure is markedly elevated, the fields show severe defects, and the optic nerve is deeply cupped. Thus it seems that the facility of aqueous outflow, which is a measure of the resistance that exists in the eye to the outflow of aqueous, is a relatively constant factor in chronic simple glaucoma; at least, it does not seem to show diurnal changes. On the other hand, it probably becomes slowly, gradually poorer as the disease advances, since previous reports on tonography# demonstrated that as a rule eyes with higher intraocular pressure and more advanced disease also had a correspondingly lower facility of aqueous outflow. This lack of diurnal changes in the facility of aqueous outflow would tend to speak against a functional, or neurovascular, mechanism as the causative or controlling factor in the drainage of the aqueous humor. On the other hand, its slowly progressive, gradually changing nature would favor organic causes. Thus it seems possible that one of the characteristics of chronic simple, wide-angle glaucoma, namely, the persistent increased resistance to the aqueous outflow, might be of an organic, or mechanical, nature.

The present study reemphasizes the practical usefulness of early morning tonometry, and also of tonography, in the diagnosis of chronic simple glaucoma. In several of the early cases of this disease intraocular pressures were in the normal or near-normal range at noon or in the afternoon, while the morning tensions were elevated. The tonographic readings, on the other hand, were in the glaucomatous range both in the morning, when the intraocular pressure was elevated, and also in the afternoon, when it was within normal limits. Thus tonography can be helpful in the diagnosis of these cases not only when the intraocular pressure is elevated, but even when it is in the normal range. However, there were a few exceptions to this rule; some of these cases of untreated chronic simple glaucoma showed normal tonographic readings, the facility of aqueous outflow being in the borderline or low-normal range. This observation substantiates the previous findings of de Roetth and Knighton [8] and of Kronfeld,[9] who reported some overlap of the normal and the glaucomatous levels. This fact does not detract from the importance and clinical

¶ Mr. Redmond Smith, F.R.C.S., helped in the gonioscopic examination.

References 4 through 6 and 8 through 10.

significance of tonography; it merely implies that equivocal values can occasionally be obtained with this new test and that, therefore, the results should be considered together with the rest of the evidence at hand. It should complement, but not exclude, the other clinical methods in the diagnosis of early cases of chronic simple, wide-angle glaucoma. The results with the water-drinking test are of interest because they aid in the understanding of the mechanics of this test and, with a new approach, substantiate the work of previous investigators.

SUMMARY

Eyes with chronic simple, wide-angle glaucoma that had not been operated on or treated and that had exhibited spontaneous or artificially induced diurnal variations in intraocular pressure did not show corresponding changes in the facility of aqueous outflow as measured by tonography. In eyes with congestive, narrow-angle glaucoma, on the other hand, the facility of aqueous outflow was related to the diurnal changes in intraocular pressure. The tonographic measurements in conjunction with the water-drinking test indicated that the intake of large quantities of water resulted in an increased flow of fluid into the anterior chamber, thus causing an increase in the rate of aqueous outflow. The clinical importance of tonography in the diagnosis of early cases of chronic simple, wide-angle glaucoma is demonstrated.

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Sir Stewart Duke-Elder gave helpful advice in my work.

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A NEW TRACHOMA CONCEPT

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Introduction
Simple Trachoma
Pathology
Criteria of Diagnosis—The Triad
Methods of Examining for the Triad
1. Follicles
2. Cicatrices
3. Pannus
Infected Trachoma
Criteria of Trachoma Cure
Differential Diagnosis
Classification of Trachoma
Proposal of a Uniform Method of Recording Trachoma
Application to Practical Trachoma Problems
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INTRODUCTION

TRACHOMA is a mild, insidious disease, frequently self-limiting, not especially infectious, comparatively harmless, the causative organism of which we accept today as a filterable virus, not yet isolated, but believed to be specific for conjunctival and corneal epithelium.

There are only two types of trachoma. The first is true, simple trachoma, as defined by the preceding statement. The second is infected trachoma, the result of an addition to the trachoma virus of one or a variety of secondary organisms. These two types are distinctly different one from the other in every pathological and clinical aspect. The failure to differentiate these two types, or the indifference toward their recognition, resulted in the mass of confusion in the literature on trachoma of the past 100 years. Writers have not yet come to an agreement on what they are talking about when they say trachoma.

It is the purpose of this article to revaluate the old textbook point of view on trachoma and to form a new, practical concept of the trachoma problem as a whole. It is based on years of personal observation in endemic areas in China, where trachoma constitutes about 50% of all eye cases that come to our free clinics.

SIMPLE TRACHOMA

To understand trachoma, it is necessary to study first true, simple trachoma. It is the fundamental question of etiology, pathology, and clinical progression of simple trachoma, not yet fully understood, that makes the whole trachoma problem

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so baffling. Lindner (1938) said: "To know trachoma one must have examined, treated, and followed up thousands of cases." Perhaps it would be truer if the word "simple" were added before the word "cases."

Pathology.—The primary and only reaction of the conjunctival tissue to the trachoma virus is a chronic hyperplasia of the lymphatic apparatus, resulting in the formation of follicular lymphomata.[2] It is not an inflammation; therefore, simple trachoma is not a conjunctivitis. There is no acute phase, and the time and mode of onset are still a subject for research. A carrier state is possible. If there is no other organism coming in to produce a new and different reaction, the conjunctiva and the trachoma virus may live on for decades in perfect balance, without any perceptible pathological changes being shown in the host tissue. A sort of equilibrium is established. If it happens that the virus is more favored by changes of certain factors in the relationship, folliculomata will make their appearance. Then, again, if the conjunctiva is able to increase its resistance to equal the virus, these lesions will disappear entirely, or leave behind some signs of the conflict, in the form of fine scarring.

All this can take place without any sign or symptom, and a person may live and die with trachoma without at any time being aware of its presence, or without its ever being discovered. The ophthalmologist can appreciate the difficulty of diagnosis in such a disease, in which signs and symptoms can run the whole gamut of the spectrum, from no detectability through stages of visibility to the slit lamp only, then to the loupe, and, finally, to the naked eye.

Criteria of Diagnosis.—Though a lymph follicle is the primary lesion of trachoma, cicatrization and pannus formation make their appearance almost simultaneously with the appearance of lymphomata. As long as the diagnosis of trachoma remains based essentially on clinical signs, this triad may be taken to form the criteria of diagnosis.

To be able to call a case one of trachoma, at least two out of the three triad signs must be present. These are, namely, (1) lymphomata, or follicles, 30%; (2) cicatrices, 30%, and (3) pannus, 40%.

The percentages are arbitrarily put down to indicate the certainty of the diagnosis. There must be at least 60% certainty to make the diagnosis stand. Any single finding alone is not trachoma. All three make trachoma with 100% certainty, and any two together can pass on trachoma with a certainty of 60% or 70%. Pannus is given a 40% value because it is considered that much more pathognomonic of trachoma. Trachoma can exist without pannus, but the diagnosis becomes doubtful indeed.

Methods of Examining for the Triad.—1. Lymphomata, or follicles, are found early in the upper retrotarsal fold. It is most important in looking for trachoma follicles to "pop out" the fornix by asking the patient to look down and pressing upward on the eyeball until the entire retrotarsal conjunctiva shows under a strong light. With tight lids, a suitable lid evertor must be used, preferably with the patient lying down. The lid conjunctiva is normal at this stage, and if this procedure of showing up the fornix is not properly carried out, the first sign of trachoma will be missed.

Trachoma follicles are simple aggregations of lymph cells without exudation. They are deeply imbedded, large, and devoid of sharp outlines. Owing to necrotic changes within, the follicles are typically soft and gelatinous, making them easily expressible with forceps.

Contrast this with the nontrachomatous follicles, such as those of inclusion conjunctivitis and all types of folliculosis, which nodules are discrete, raised, transparent, hard, and difficult to express. This difference is only clinical, for histologically all follicles appear the same. The more conspicuous and well-arranged the follicles, the less likely they are to be trachoma.

The presence of follicles brings another early sign of trachoma, namely, the blurring of the fine vessels in the fornix due to the conjunctiva of the retrotarsal fold becoming thickened and losing its transparency. This blurring of the fornix often hides the follicles underneath; so it sometimes becomes the only sign showing in the fornix.

This blurring of the fornix vessels must not be mistaken for papillary hypertrophy. Papillae are formed by the conjunctival epithelium being thrown into minute folds, causing the upper palisade of vessels of the lid to become blurred and presenting a velvety or granular appearance, which by this time may be noted in the lid conjunctiva beyond the retrotarsal fold. These are due to chronic irritation—an inflammatory reaction. So when we see papillary hypertrophy, secondary organisms have already come in to change simple trachoma into infected trachoma.

2. Cicatrices are fine white star-shaped or linear scars in the retrotarsal fold following immediately the appearance of follicles. As the follicles break down in necrosis, healing takes place by scarring, which is so delicate that it may, in turn, become absorbed and disappear. In simple trachoma there is a process of new follicle formation, necrosis, scarring, and absorption continuously going on. Total disappearance of the follicles and cicatrices can occur when the virus loses its foothold in the equilibrium, provided there has been no secondary bacterial invasion. Cure of simple trachoma takes place thus by complete disappearance of all signs, and the conjunctiva of the fornix reverts to a perfectly normal one. Relapse of trachoma is likewise heralded in by the reappearance of follicles and cicatrices. Trachoma cicatrices are therefore nonpermanent, nor do they appear at the same spot all the time.

Examination for cicatrices also requires the full exposure of the fornix to good light. We must differentiate this delicate scarring of simple trachoma, caused by a virus, from the thick coarse scarring of the lid caused by an inflammatory reaction. The classic boat-shaped tarsus is found only after prolonged secondary infection. Simple trachoma never produces heavy scars which lead to deformity.

3. Pannus is a thin film composed of lymphocytes and new-formed vessels between the corneal epithelium and Bowman's membrane, chiefly located at the upper clear cornea just beyond the limbus. The corneal epithelium, being a continuous layer of cells from the bulbar conjunctiva, is the primary site of invasion. Bowman's membrane and the cornea proper are secondarily attacked only later. As to why the location of the upper cornea is specifically chosen there is so far no satisfactory explanation. It is not entirely due to mechanical irritation of the lids.

The pathology of pannus formation is analogous to and simultaneous with what takes place in the fornix. The primary lesion here is likewise the microscopic lymphoma, which is followed by scarring and absorption. A similar equilibrium is also established here between host tissue and the virus. In the absence of any secondary organism to upset this equilibrium, the lesion would stay limited to the corneal epithelium. Any destruction of Bowman's membrane or the cornea proper would indicate that an inflammatory process has also come in to take part, and the picture becomes a combination of pannus and keratitis.

New-formed vessels, though an integral part of pannus, are not specific to trachoma. Any irritation of tissue will call forth an increase of blood supply. In the fornix, already rich in vessels, hyperemia is accomplished by vasodilatation. In the avascular cornea it is by vascularization. As the trachoma virus is a mild organism, the irritation is mild, and the reaction is therefore minimal.

It requires some experience to observe the pannus of simple trachoma. Good focal lighting and a loupe are always necessary. The slit lamp must be used as a final arbiter in doubtful cases. When a pannus is visible to the naked eye of the observer, the trachoma is no longer simple but has gone into the infected category.

The earliest observable sign of trachoma pannus appears as a very fine stippling, or as a diffuse haze at the upper crescent of clear cornea just below the limbus. It corresponds to the stage of lymphoma formation and scarring in the fornix. Vascularization of this area immediately follows in the form of tiny vessels coming down from the plexus circularis that normally forms around the limbus. These appear through the loupe as parallel, straight, delicate twigs of unequal lengths, some terminating in grayish dots in the film of haze. With the slit lamp they are best seen by the beam of light reflected from the iris surface. The vessels appear black or dark-red silhouetted against the illuminated background. Some terminate in tiny loops, and roulettes of blood corpuscles can be seen coursing through them in single file.

The observer must be careful to differentiate what is normal limbus from what is pannus, as the demarcation is not always a sharp one. In Chinese eyes, the limbus is especially broad, coming down sometimes over one-fifth of the cornea and ending in a jagged line. The normal terminal capillary network, together with the translucent, grayish striae of the scleral spur, can confuse one not used to examining these eyes. In light-colored eyes this difficulty in observation hardly exists.

One type of vascularization is particularly misleading—the eczematous pannus. This appears all around the limbus more or less equally. In case of doubt, one must always compare the vessels at the lower limbus with the upper portion under the slit lamp. The presence of vessels below, especially if they are more numerous than above, shows that the pannus is probably not trachomatous.

INFECTED TRACHOMA

Infected trachoma must be distinguished from simple trachoma as an entirely separate entity. It is the trachoma described in the textbooks. It is the trachoma we see every day. It is the trachoma the majority of authors meant when they wrote anything about it. MacCallan's (1908) four-stage classification could apply to infected trachoma only.

A great number of organisms can live together and flourish with the trachoma virus to produce various degrees of damage to the host tissue. Many factors determine the virulence. In mild cases the picture of infected trachoma will be borderline to that of simple trachoma, and one can hardly tell when simple trachoma ends and

Differential Diagnosis of Folliculosis, Simple Trachoma, Infected Trachoma, and Chronic Conjunctivitis

	Folliculosis	Simple Trachoma	Infected Trachoma	Chronic Conjunctivitis
Etiology	No organism found	A specific virus; mildly contagious (?)	Virus plus bacteria; contagious	Bacteria; irritants
Pathology				
Primary lesion	Lymphatic hyperplasia—follicles	Lymphatic hyperplasia—follicles (no histological difference)	Follicles and granulations	Granulations
Tissue reaction	1. None 2. Catarrhal exudate 3. No pannus	1. None 2. Catarrhal exudate 3. Pannus	1. Inflammatory 2. Allergic and exudative 3. Vascularization more marked	1. Chronic inflammation 2. Allergic and exudative 3. Even vascularization all around
Progress	Spontaneous healing	In equilibrium Normal conjunctiva→follicles;→bacteria→Virus pannus └Cicatrices┘	Chronic inflammation	Chronic inflammation
End-product	1. Absorbed 2. No scarring (?)	1. Absorbed 2. Cicatrices, coming and going	1. Absorbed 2. Scarring, tends to remain extensive and deep	1. Absorbed 2. Scarring
Complications	None Harmless disease	None Never causes blindness	Keratitis, ulceration, entropion, etc.; results harmful, leading to blindness	Usually none; may vary according to virulence and resistance
Symptoms	1. None 2. Mild irritation 3. Onset never acute	1. None 2. Mild irritation 3. Onset never acute	1. Usually present 2. Degree varies 3. Onset probably always with an acute phase	1. Usually present 2. Degree varies 3. Onset probably always with an acute phase
Differential diagnosis				
Common signs	1. Follicles discrete, hard, raised, distinct, transparent 2. Conjunctiva normal and transparent, with vessels distinct 3. Lower fornix more frequently involved, like string of pearls 4. No pannus	1. Follicles soft, gelatinous, confluent 2. Conjunctiva becomes blurred, and vessels indistinct 3. Upper fornix primary site; lower usually normal 4. Delicate pannus, upper cornea	1. Papillary hypertrophy covering up follicles 2. Conjunctiva inflamed 3. Upper and lower fornices involved; upper predominant 4. Pannus becomes exaggerated	1. Granulations 2. Conjunctiva inflamed 3. Lower fornix predominant 4. Eczematous type of pannus, if any
Special signs	Only follicles	The triad	The triad and inflammation	Only chronic inflammation
Response to treatment	1. No response to sulfonamide drugs and antibiotics 2. Astringents such as Cu and Zn helpful		Practically all secondary organisms are eliminated by sulfonamide and antibiotics; astringents helpful later	
Criterion of cure	A normal conjunctiva	A normal conjunctiva or fine cicatrices	Scarring more likely than a normal conjunctiva	Scarring more likely than a normal conjunctiva

secondary infection begins. On the other hand, infected trachoma can go through all the four stages, resulting in deep conjunctivitis, thick scarring, entropion, keratitis, ulceration, and subsequent blindness.

The exact relationship between a pathogenic organism and the relatively nonpathogenic trachoma virus will not be thoroughly understood until the latter can

be isolated for study. It really matters not which is the first to take occupancy of the conjunctival tissue and which is the secondary invader. The final clinical picture is the same.

It is possible to change infected trachoma into simple trachoma simply by taking away the infection, provided no permanent damage has yet been done. By the use of antibiotics or sulfonamide drugs, the infection is removed and simple trachoma is left.[16] This, again, can be changed back into infected trachoma by reintroducing the particular organisms. I believe that when we find the specific anti-trachoma-virus drug, it will also be possible to take away simple trachoma from infected trachoma and leave behind only the conjunctivitis.

CRITERIA OF TRACHOMA CURE

Trachoma is considered cured when the triad signs are broken up so that less than 60% of points can be given. When two of the three cardinal signs have been removed, the diagnosis can no longer stand on the remaining leg. Usually all three signs disappear in the cure of simple trachoma, and a normal conjunctiva is left.

In infected trachoma, the criterion of cure is essentially the subsidence of inflammation. This converts it into simple trachoma. Scarring will be left behind as a sign of healing, the amount varying according to the depth and the time the infection has been going on. In pannus, there remain the attenuated, empty, and sclerosed vessels, which form of scarring will never become entirely absorbed.

DIFFERENTIAL DIAGNOSIS

In daily clinical work, four conditions are frequently seen which must be differentiated one from another. These are, namely, in consecutive order, folliculosis, simple trachoma, infected trachoma, and chronic conjunctivitis. The differential diagnosis of these four conditions is summarized in the accompanying Table. For other conditions, the reader is referred to standard textbooks.

CLASSIFICATION OF TRACHOMA

Trachoma can be classified simply into two categories, (1) simple trachoma and (2) infected trachoma.

Simple trachoma requires no further subdivision. The word "simple" is sufficient to denote mildness, absence of infection and complications, and possibility of complete self-healing. It has no stages of clinical progression except that the equilibrium may shift back and forth.

In recording infected trachoma, I have used MacCallan's four-stage classification but have found that it is not sufficiently descriptive for either academic or clinical purposes. The division is based on the amount of inflammation present, and it uses the degree of cicatrization to denote the stages. This system does not convey any definite or consistent picture to the mind of the reader. Tr I, by definition, is not trachoma. Tr II, Tr III, and Tr IV are not clean-cut stages. Obviously, it is more desirable to have a system which will indicate at once the degree of inflammation present, the site and amount of tissue involved, the nature of the cellular changes, and complications, if any, than a series of numerals to show only how much scarring has occurred.

PROPOSAL OF A UNIFORM METHOD OF RECORDING TRACHOMA

A special trachoma sheet should be used by clinics which routinely handle many cases. A sample of such a trachoma sheet follows. The diagram of the right (R) and left (L) eyes shows at a glance the condition seen in the patient's initial visit. The dated columns show progress as time goes on. Plus (+) and minus (—) signs and a system of ophthalmic shorthand can be used. A space is left for any special notes or drawings.

TRACHOMA SHEET

Name..... Age..... Sex.....

Address .....

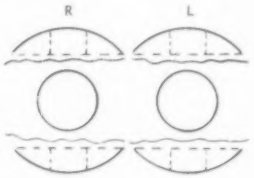
Organization or School.....

Purpose of Examination.....

Date .....

Occupation .....

Examining Doctor.....



Diagnosis 1. Simple Trachoma

2. Infected Trachoma

3. .....

Date	Complaints and Symptoms	Type of Lesion	Pannus	Vision	Conjunctivitis	Cicatrices	Rx	Complications

Space for Special Notes:

EXPLANATION OF USE OF TRACHOMA SHEET

Purpose of Examination.—This is to be filled in with such words as "routine," "annual px," "emigration," "health project," or "special research," as the case may be.

Diagnosis.—Either (1) or (2) is to be crossed out; (3) is left for such words as "nonspecific conjunctivitis," "folliculosis," or other eye conditions—"primary optic atrophy," "glaucoma," etc., whichever may be relevant to the case. I use a rubber stamp "No trachoma" as a routine when the case is found to have no trachoma, purposely to indicate that trachoma signs are specifically looked for in every case.

Date.—The date is to be stamped on each separate visit. The initial findings should be put down on the first date of visit for subsequent comparison down the column.

Complaints and Symptoms.—Words such as "nil," "tearing OS," "smarting OD," "sandy OU," "AM dscj," "Hda," and "Hv lids" can be used for each such condition complained of.

Type of Lesion.—F indicates follicular; Pap, papillary hypertrophy; Gel, gelatinous; C, cicatrization; G, Gel, follicular and gelatinous, etc.

Pannus.—In addition to indicating the amount of pannus in the diagram, the + and — system should be also used. The horizontal and vertical lines divide the upper and lower cornea (C) of the right (R) and left (L) eyes, respectively. Examples follow.

= No pannus upper C; lower C not examined (hereafter a blank space means not "negative" but "not examined")

= Upper and lower C examined and limbuses found to be hazy but a pannus could not definitely be said to be present

= Mild pannus upper and lower C (therefore probably eczematous) (The + sign really should be reserved to indicate that the slit lamp is used in finding the pannus positive)

= Slit lamp: Upper C positive; lower C not examined

= Slit lamp: Upper C positive; lower C pannus definitely absent

= Upper C OU positive; observation by 10 × loupe and focal light

= R upper C pannus can be seen with naked eye; L upper C negative (a monocular case)

= Pannus of both upper C extending below half of cornea

= Both C's totally covered with pannus and opacities; pupils and iris invisible

The use of the + and — signs for indicating degrees of pannus requires further explanation.

= Not examined

(sl0) = No pannus, using the slit lamp for observation

(10×) = No pannus, using only 10 × loupe for observation

± (sl±) = Hazy limbus, but vessels not definite, using slit lamp for observation (If 10 × loupe only is used, put down "10 ×")

\+ = Pannus positive by slit lamp (+ is reserved to mean slit lamp used)

\+ + = Pannus positive by 10 × loupe (+ + is reserved to mean loupe is used); slit lamp not necessary

\+ + + = Pannus visible to naked eye of examiner

\+ + + + = Pannus covering more than half of the cornea up to total opacity

Vision.—This means unaided visual acuity for distance and reading charts; both eyes are tested separately. If glasses are used, it should be designated "c̄ gl," and the Rx formula put down in the space below.

Conjunctivitis.—This is taken to mean the amount of secondary infection present.

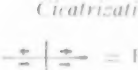
= No inflammation (a quiet case)

= Mild redness and discharge from upper lids; lower lids of both eyes normal

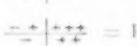
= L. eye, especially upper lid, more than moderately inflamed, with early involvement of lower lid; R eye quiet (though not trachoma-free)

= R eye severely inflamed, incapacitating the patient in his work; L eye moderately inflamed

Cicatrization.

 = Fine cicatrices in upper fornix OU; fornix has to be "popped out" for observation

= Cicatrization extending beyond the upper fornix OU (MacCallan Tr II)

 = R upper lid mild scarring (Tr II); R lower lid free; L upper lid moderate scarring (Tr III); L lower fornix showing line of scarring

= Total scarring; healed or spent (Tr IV)

Treatment (Rx).—This space is for words such as $CuSO_4$ 3X/wk.; $ZnSO_4$ t. i. d.; Trisulfazine 2, t. i. d.; Aureo. oint. q. noc., etc.

Complications.

Trich = 4 inturning eyelashes in right upper lid nearer temporal side; 6 inturning lashes, L. lower lid, in middle

Entrop = R upper moderate entropion; R lower normal position; L total entropion with inturning of all lashes

Other complications, such as xerosis corneae, ectasia, and ulceration, can also be put down in this column.

Diagram of the R and L Eyes.—This is probably the most important information in the whole trachoma sheet. In the upper and lower lids, four locations, namely, the temporal, the middle and nasal thirds of the lid conjunctiva, and the fornix, are mapped out in dotted lines to show exactly where the lesions are found. The doctor needs only to use a pen to shade that portion to be indicated.* He can also show the type of lesion by dots, lines, or circles, or by alphabetic shorthand.

The two circles in the diagram represent the R and L corneas. Here can be shown the amount of pannus present and other corneal complications, such as ulcer, keratitis, or leucoma adherens, by filling it in with a pen.

* The Chinese Medical Association Committee on Trachoma has proposed and adopted this method, but only the upper lid is diagrammed, as the Committee does not think the lower lid is important in trachoma.[9]

APPLICATION OF THE NEW TRACHOMA CONCEPT TO PRACTICAL PROBLEMS OF CONTROL AND TO INTERNATIONAL QUARANTINE MEASURES

The World Health Organization Expert Committee on Trachoma [13] makes a statement regarding this question: "The Committee wishes above all to make it quite clear that in the present state of knowledge, trachoma is to be considered as only slightly contagious." Infection is transmitted from a conjunctivitis that is producing a discharge. It is infected trachoma that is contagious. Simple trachoma is probably noncontagious. If contagiousness is the keynote to all the problems of trachoma control, the emphasis should then be on the control of conjunctivitis rather than on trachoma itself.

Hong Kong is a port of clearing for emigration, from whence people leave for Europe, the South Seas, and the Americas. It is an endemic area for trachoma. Every country has its medical officers to carry out the general physical examinations and to look especially for trachoma in emigrants before embarkation. What exactly constitutes the diagnosis of trachoma is left much to the interpretation of the examiner. The instructions given on the subject are not clear-cut. The stamp of trachoma means that the emigrant's sailing is held up for treatment until his trachoma is "apparently cured." Then, "after all treatment has ceased, such emigrant shall be deferred for 6 months and then be re-examined and if still 'apparently cured' be passed." †

In the light of a new trachoma concept, the regulations governing international trachoma quarantine measures should be modified and be brought in line with present knowledge. The diagnosis of simple trachoma need not be a reason to detain any traveler. With modern chemotherapy infected trachoma can be arrested in a relatively short time, and in the length and method of quarantine this fact should be given due consideration.

It may be suggested that for routine clinical work in trachoma endemic areas, the use of the loupe and focal lighting be admitted as sufficient to determine whether a pannus is present or not, for the reason that not all workers have access to a slit lamp and that in not all places where the examination is carried out can a slit lamp be used. A suspected case of trachoma with a pannus "± loupe" or "+ loupe" is only an academic question. So for practical purposes, such as examination of emigrants or school children, the 2 + (++) must be put down in order to give the 40% points in diagnosis.

TREATMENT OF TRACHOMA

In simple trachoma expression of any large follicles and use of mild astringents are sufficient. Copper sulfate (blue stone) has both a mechanical and a stimulating effect and is still a good stand-by. In infected trachoma, the conjunctivitis should be treated first with antibiotics and sulfonamide drugs. In complicated cases surgery may be necessary. In borderline cases only periodic observation is required. With such an understanding and modern methods of treatment, trachoma is not such a horrible disease as it was once regarded. Trachoma can be eliminated.

† Quotation from copies of Medical Instructions given to me by the Office of Canadian Immigration, 1952, and by the American Consulate General, 1939.

SUMMARY

The pathology of simple trachoma is a quiet hyperplasia of the lymphatics of the conjunctival epithelium. It is not an inflammation; therefore trachoma is not a conjunctivitis, and there is no acute phase. The primary lesion is a follicle, located specifically in the upper retrotarsal fold and the epithelium of the upper cornea. Scarring and vascularization are reactions following this follicle.

The cause is a virus, of which little is known. Until this virus can be isolated for study, there will be many questions waiting to be answered. The presence of the trachoma virus incites only a mild reaction in the host tissue, which reaction may or may not be detected. An equilibrium is established among the normal conjunctiva, the trachoma follicle, and its products. The shifting of this equilibrium is a characteristic of trachoma which is influenced by a number of factors not yet quite clear to us. The invasion of a secondary organism will cause a marked disturbance in the equilibrium—even to breaking it up and changing it into a different pathological product, to be called infected trachoma. On the other hand, less important factors will produce slighter shifting in one or the other direction.

The clinical criteria of trachoma diagnosis are the triad signs, namely, follicle (30%), pannus (40%), and cicatrices (30%). At least two out of the three (60 to 70%) must be present for a case to be called trachoma. The criterion of cure is the breaking up of this triad to a point lower than 60%.

The classification of trachoma is given: (1) simple trachoma, as described above, and (2) infected trachoma, which is the trachoma described in textbooks and writings, and which is the trachoma we recognize in our clinics. These two types differ distinctly from each other in etiology, pathology, symptoms, and treatment. We have heretofore not given this distinction adequate thought, a fact which explains why there is so much confusion in the trachoma literature of the past.

A uniform, simple method of recording trachoma is proposed for the purpose of study, research, and practical use among international workers. Its application in public health and quarantine problems is discussed.

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ANGIOID STREAKS

Tears in Bruch's Membrane or Pigmented Choroidal Vessels(?)

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FEW MORE arresting or puzzling ophthalmoscopic pictures exist than that of the fully developed case of angioid streaks. Splashed across the fundus, a great network of jagged brownish bands, some broader than the largest retinal veins and others tiny anastomosing threads, they take origin from the neighborhood of the disc and extend more or less radially toward the periphery, resembling nothing so much as a system of anomalously pigmented vessels. Like vessels, they branch, they anastomose, and they tend to taper as they approach the periphery. Like a system of vessels, they show a more or less uniform distribution, a basic pattern found in case after case with only minor variations, putting one in mind of some kind of fixed anatomic structure.[1] Pigmentation, on the other hand, is suggested by their color, their serrated edges, the marked changes in width, and the frequent presence of other types of fundus disturbance of an unquestionably pigmentary character. Bedell * declared: "The more I examine these cases the more I tend to think the dark lines are migrated pigment." Indeed, since their first discovery, in 1889, the streaks have been regarded as pigmentary or vascular or both by the majority of observers, although few have agreed as to their exact pathogenesis. In recent years, however, a theory has gained wide acceptance which rejects altogether the pigmentary and vascular hypotheses and seeks to explain the entire fundus picture in terms of minute rents in a degenerated Bruch's membrane. First advanced in 1917, this idea received scant notice because of its incompatibility with the clinical findings, until 1929, when attention was focused upon a condition outside the eye altogether, pseudoxanthoma elasticum. Because both the skin lesions and the eye findings, so often present together, could be put on the same etiologic basis, that of a familial and premature degeneration of the elastic tissues, the membrane-tear theory of angioid streaks enjoyed an enthusiastic revival. Renewed efforts were made to reconcile the old theory with the fundus signs. When it was found pathologically that the membrane was actually ruptured in several cases, little doubt remained that the mechanism of streak formation was at last understood. Two facts, however, were forgotten. First, streaks occur without demonstrable breaks in Bruch's membrane, and, second, breaks in Bruch's membrane occur without demonstrable streaks.

Whatever the hypothesis, many unanswered questions arise, but in none so many as in the tear-in-membrane theory. An attempt is made here to underline some of its inconsistencies and to put forward another explanation, without pathologic evidence, it is true, but one which seems more adequate from the clinical standpoint.

* Bedell, A. J., in discussion on Clay.[3]

especially in the light of certain observations made in the two cases presented. These observations have been confirmed by another ophthalmologist. One has not been recorded before; others have appeared in the literature, but their significance seems to have escaped attention.

CLINICAL PICTURE

Scholz's analysis of the literature in 1941 is the lastest and most comprehensive.[2] According to him, cases have been reported from all parts of the world, are divided about equally between the sexes, occur most commonly between the second and fifth decades, reaching a peak in the fifth decade, and show a statistically significant excess in myopes. Except for cases with associated fundus changes, such as macular degeneration, the fields are normal. The streaks lie unconnected with and below the retinal vessels, at a level variously estimated to coincide with the pigment epithelium, Bruch's membrane, or the choroid. Sometimes, thread-like, they may be four or five times as wide as a retinal vein. Indeed, great changes in width may occur in the same streak. With edges usually irregular or serrated, they may radiate spoke-like from the region of the disc or interconnect to such an extent as to form a mosaic. Their origin lies close to, but at a somewhat variable distance from, the disc margins and may take the form of a network surrounding the disc or of a partly broken circle. The disc may be completely enclosed by a ring, but not invariably by any means, Scholz notwithstanding. Of the 188 cases reviewed by Scholz, the color of the streaks had been described in 103. According to him, in 65 cases the color was brown or reddish-brown; in 27, gray, and in the rest, red, black, white, or gray-brown. Trauma, usually contusion, figured in 24 cases, leading to fundus hemorrhage, with impaired vision, and ophthalmoscopic examination. The macula was abnormal in one or both eyes of 140 patients. Of these patients, 35 showed recent macular hemorrhages; 19, scarring; 18, abnormal pigment, and the remaining 23, holes in the macula or exudate or "specific forms of retinitis, such as disciform degeneration or retinitis circinata." Retinal hemorrhage was seen in 65 patients, and "choroiditis" of one type or another, in 70.

Pigmentary changes of all kinds occur throughout the fundi, varying from large, irregular deposits to a fine stippling of the maculas or peripheral areas. The latter is perhaps more commonly reported than any other associated finding and appears to be peculiar to the disease. Sometimes the stippling is red instead of brown or black and must then be difficult to differentiate from the punctate hemorrhages,† which have often been observed in much the same locations.

Whitish areas of many kinds are found. Edema, lipid deposits, often forming retinitis circinata, exudates, drusen, and patches of chorioretinal atrophy are among the causes. The atrophic areas are often circular and are most apt to lie in the course of a streak, which may pass over them or be interrupted. Circumpapillary atrophy resembling halo senilis is common. There is also a tendency for atrophy to develop along the sides of certain streaks in more advanced cases,[3] an atrophy which is very similar clinically to the perivascular choroidal form illustrated in Wilmer's [4] "Atlas Fundus Oculi." Zentmayer [5] expressed the opinion that the widespread choroidal sclerosis and degeneration found in his case after many years of observation might

† References 1, 3, 7, 15, and 75.

be the usual terminal stage of the disease. Other examples of extensive choroidal degeneration are seen in the case of Coppez and Danis,[6] possibly Batten's first case,[7] and certainly the second case to be presented here.

The maculas may show exudates, hemorrhages, or any form of pigment disturbance. There may be a disciform type of degeneration or simply bands of connective tissue, like retinitis proliferans. Similar connective tissue overgrowths may line the edges of the streaks for considerable distances or form on their ends as whitish tails. While the course of the macular disturbance is often rapid before the development of scar tissue, the streaks themselves may remain unchanged for decades. With but few exceptions, the changes that do occur are gradual. Apparently, the streaks may lengthen or shorten, grow broader or narrower, become more or less numerous, or disappear altogether.‡ Pressure upon the globe has been reported by Clay to cause them to disappear,[3] an observation nobody has confirmed and some have denied.§ Often red in the early stages, they may become brown or black. By 1941, according to Scholz, 46 cases had been followed more than a year. Of these, 33% showed an increase in number, 56% no change, and 10% a decrease.

Reported monocularly in only three cases,‖ the condition is thought to be transmitted as a recessive hereditary character, like pseudoxanthoma elasticum.¶ Scholz stated in 1941 that 18 cases had been described in which siblings were similarly affected. In four cases the parents were consanguineous.

Frequently accompanying the disease are three separate systemic conditions, generalized vascular disease, Paget's disease, and pseudoxanthoma elasticum. Curiously, the last two have never been reported as occurring together.

As far back as the last century, Haab # and de Schweinitz [10] noted the high incidence of generalized circulatory disturbance. Holloway [11] found it in 23.3% of 60 cases. Verhoeff [12] pointed out that of the six patients with undoubted cases pathologically studied, four died of cardiovascular-renal disease. Numerous reports stress the high percentage of siblings of typical cases who have vascular disease. Peripheral vascular disease, also common, will be discussed later.

The coexistence of Paget's disease with the streaks had been reported 12 times by 1941. According to Scholz, Paget's disease was found in 9% of 139 cases of the streaks, and the streaks in 8% of 65 cases of Paget's disease.

As for pseudoxanthoma elasticum, between 1941 and the time its association with the streaks was first recognized (1929) 139 cases of the streaks had been described, of which 59% showed the skin condition.[2] Goedbloed [13] collected 67 cases from the literature, 57 of which had pseudoxanthoma. In an analysis of 100 cases of the latter condition taken from the literature, Sandbacka-Holström [14] stated that 87 showed angioid streaks. The skin lesions occur typically on the neck, cubital fossae, axillas, groin, and popliteal spaces. The skin in the affected areas becomes lax and leathery and presents small yellowish or orange "tumefactions," sometimes referred to as papules, which tend to form linearly and coalesce into

‡ References 3, 5, and 74.

§ References 8 and 23.

‖ Reference 24. Isayama, cited by Scholz.[2] References 30 and 31.

¶ References 9, 13, 25, 30, and 31.

Haab, cited by Holloway.[11]

plaques. Pathologically there is a degeneration, with fragmentation of elastic fibers and deposits of calcium in the middle and deep layers of the corium. Similar abnormal deposits of calcium, as well as iron, have been demonstrated in Bruch's membrane in cases of angioid streaks.[15]

HISTORY

Since 1889, when the streaks were first described by Doyne,[16] more than 200 cases have been reported. Doyne's patient came to him after a contusion to one eye. Extensive deep fundus hemorrhages led him to attribute the streaks to changes in the pigment epithelium secondary to hemorrhage. Plange,[17] who published the second report in 1891, and Knapp,[18] who published the third and called the streaks "angioid," agreed that hemorrhage must be the cause. Many of the early writers held the same view.

In general, attempts have been made to explain the streaks in four different ways. In addition to the hemorrhagic theory, hypotheses assumed that vessels were the basis for the streaks, that folds in some layer of the fundus were involved, and, finally, that tears in Bruch's membrane were responsible.

The vascular theory took several forms and was especially favored after Lister,[19] in 1903, had demonstrated abnormal vessels in the deep layers of the retina of an eye with long-standing endophthalmitis. Some felt that the vessels, retinal or choroidal, were newly formed as part of an inflammatory process.* Others held that they were congenitally anomalous.† Still others believed they were not anomalous but were choroidal vessels which had become visible through pathologic pigmentation.‡

Walser [24] and Law [25] attributed the streaks to folds in the retina; Alt [26] and Guist,[27] to folds in the pigment epithelium, and Verhoeff,[28] to folds in the choroid, a view which he later abandoned.

The theory of tears in Bruch's membrane was first expounded in 1917 by Kofler [29] because of the resemblance of the streaks to myopic tears. At first neglected, the theory received a new impetus when Grönblad,§ in 1929, reported two cases of angioid streaks with a skin condition diagnosed by Strandberg as pseudoxanthoma elasticum (Grönblad-Strandberg syndrome). On the strength of this association, Grönblad postulated a systemic degeneration of elastic tissues, including Bruch's membrane. Marchesani and Wirz [32] soon after published similar conclusions, which have been accepted by the majority of writers since. The skin disease was first described by Balzer [33] in 1884, named by Darier [34] in 1896, and reported in association with an unknown fundus disorder in 1903 by Hallopeau and Laffitte,[35] who considered the possibility of a connection between the two.

Paget's disease was first linked to angioid streaks in a case report by Rowland [36] in 1929, and later by Terry,[37] in 1934, who collected five cases from the literature and added four of his own.

Six pathologic studies have been done on well-authenticated cases. The first, Benedict's,[38] in 1937, revealed no significant pathology. The second, Law's,[25] in

* References 6 and 20.

† References 21, 22, and 23.

‡ References 1, 3, 7, 11, 50, and 71.

§ References 30 and 31.

1938, seemed to support the theory of folds in the retina with accumulated pigment debris from the uvea, but the findings were open to question because of an excessively long period of fixation, a circumstance which Law himself admitted could produce very similar changes. No other significant pathology was evident, however, and the membrane of Bruch was intact.

On the other hand, the pathologic examinations of Bock,[39] in 1938; of Hagedoorn,[40] in 1939; of Klien,[15] in 1947, and of Verhoeff,[12] in 1948, revealed basophilia and tears in Bruch's membrane, as well as changes in the choroidal vessels, interpreted by Hagedoorn as peculiar to the condition of angioid streaks and by Klien as simply an ordinary, though premature, kind of "involutionary sclerosis." While Bock and others doubted that small rents could be seen through an intact pigment epithelium, and therefore postulated corresponding tears in the latter, Hagedoorn, Klien, and Verhoeff, often unable to find any disturbance in either the adjacent pigment epithelium or the choroid, concluded that the degenerated membrane must be opaque and that this opacity brought out the choroid-exposing tears by contrast. Most authors put down the hemorrhages and other associated lesions to injury to the choriocapillaris caused by rupture in a membrane not only degenerated but calcified as well. Changes between Bruch's membrane and the pigment epithelium similar to, if not identical with, those of disciform degeneration of the macula were described.

REPORT OF CASES

Case 1.—On March 18, 1952, V. N., a 34-year-old white man in good general health, presented himself for examination because of blurring and a central black spot in his right field of vision. Thirty-six hours previously he had been struck across the right eye with moderate force by a baby's milk bottle. His symptoms had appeared immediately and had not changed. That the force of the blow had not been great was indicated by the complete absence of external signs of contusion. With a −6 D. correction before each eye, his vision was 20/100 in the right eye and 20/20 in the left eye. He was unable to fix centrally with the right eye. Examination of the fundi revealed typical angioid streaks in each eye, brownish-black, varying greatly in width, but with the largest twice the size of a retinal vein near the disc, and radiating generally toward the periphery, with many branchings and anastomoses. About the discs the networks were denser but did not form a ring. Nor was there any chorioretinal atrophy in the neighborhood of the discs or elsewhere. Apart from the streaks, the most striking finding was extensive deep hemorrhages in the posterior polar region of the injured eye. Dark-red and with clearly defined edges, they appeared to be choroidal and were arranged in large patches close to the disc, above and to the temporal side, where they covered the macular region. Beneath the hemorrhagic areas, several streaks were seen to disappear. The left fundus showed no sign of hemorrhage, past or present.

An unusual feature was the curious form taken by the hemorrhages in several places. Well shown in Figure 1 are three linear hemorrhages about 1 D.D. temporal to, and more or less concentric with, the disc. The uppermost of the three extends from the lower border of the hemorrhagic area in the macular region and ends about 1 D.D. below in a small angioid streak running almost at right angles to it. A similar hemorrhagic streak, somewhat broader and shorter, continues downward, slightly closer to the disc than the first, but originating from the same pigmented streak in which the first ends. A third linear hemorrhage extends inferiorly from the same pigmented streak near its peripheral end. The most remarkable thing about these hemorrhage formations is their extraordinary similarity in course and form to typical angioid streaks. Not only does their width correspond but also their irregular edges, more lobulated than serrated, seem identical, as is nowhere better shown than in comparing the hemorrhagic streaks just described with the pigmented streaks passing horizontally from the left disc toward the macula near the midline in Figures 2 and 3. Not unlike these linear hemorrhages

is the finger-like extension rising above the main mass of macular hemorrhage. In all four linear formations is seen a tiny dark thread-like core. What the photograph of the right fundus, unfortunately, does not show are two large angioid streaks, one leaving the neighborhood of the disc at 12 o'clock and passing directly above, and the other passing diagonally downward and temporally from the region of the disc at 7 o'clock, both of which became converted abruptly to red hemorrhagic streaks about halfway to their terminations, 3 to 4 D.D. toward the periphery. They continued forward a bright-red color, but in course and width remained totally unaltered. That these red streaks, as well as the four previously described, were hemorrhagic, and not sim-

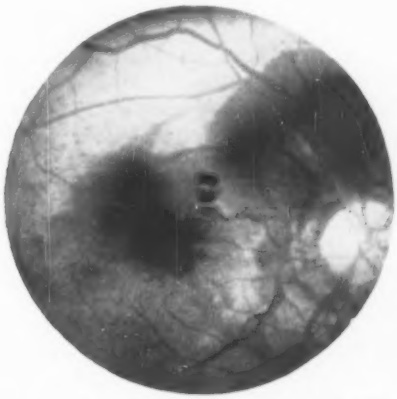

Fig. 1.—Three linear hemorrhages 1 D.D. temporal to and concentric with the disc.

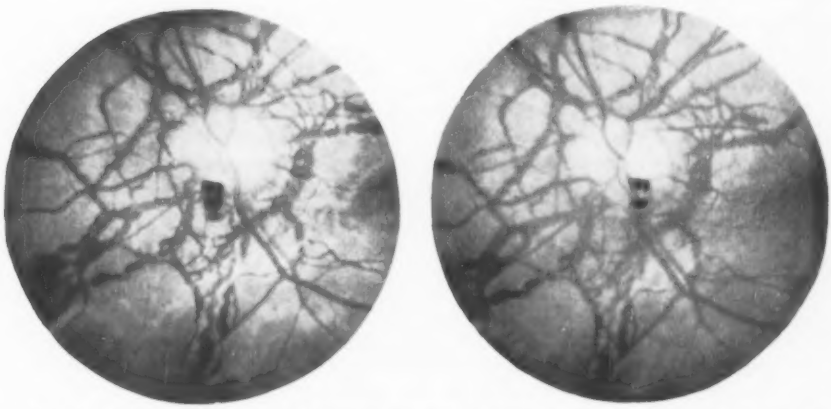

Fig. 2.—A large vertical angioid streak outlining a choroidal vessel is seen below the disc. Several streaks seen to lie behind choroidal vessels at crossings.

Fig. 3.—A streak approaching the macula from above is ensheathed with connective tissue.

ply red angioid streaks, sometimes reported in the literature, is suggested by their complete absence in the uninjured eye and proved by their gradual absorption with the main hemorrhagic masses while under observation during the subsequent months. Except in the macular region, all the hemorrhages were absorbed without leaving a trace, much less pigmented streaks, as some authors have described. In the macula itself there developed a T-shaped band of connective tissue, its stem pointing toward the disc, which seemed slightly raised above the retinal surface, as in the usual retinitis proliferans.

After about six weeks the macular scar had become stationary and the hemorrhages smaller and darker. Four months after the first visit only small faint pinkish tints remained at the bleeding sites. One year later all signs of hemorrhage had disappeared except for the macular scar. Vision remained unchanged.

Associated fundus lesions, which were stationary during a year of observation, were black stippling, in places a flaking, involving the macular and peripheral regions, and white bands ensheathing two pigmented streaks approaching the left macula, the uppermost of which is just visible in Figure 3. An excellent view of a choroidal vessel exposed inside a streak is afforded in Figure 2. The streak is broad and runs vertically below the disc. For considerable distances the streak, as outlined in black, intimately follows the vessel, conforming to every twist and turn. Other findings frequently noted in the literature, such as drusen (retinal or in the nerve head), exudates, large pigment deposits, and punctate red areas, said by Bedell to be almost a constant feature, were absent.

Of special interest are the three observations that follow. One has not been made before, and all three have been verified by another ophthalmologist.

First, in many places in both fundi choroidal vessels were seen unmistakably to cross above, not below, the streaks. Figure 2 shows this about 1 D.D. from the disc along the 5 o'clock meridian. The superimposed choroidal vessel can be seen on both sides of the streak and followed to its branchings, the whole surrounding network of which it is a part being faintly, but unquestionably, visible. Similar crossings of the streaks can be made out at 2 and 3 o'clock about the same distance from the disc. Many others, some even more distinct, were seen in the unphotographed parts of the fundi.

A second finding, seldom brought out in the literature, was the appearance of three larger streaks, running more or less parallel from near the left disc at 7 o'clock and ending inferonasally about 3 to 4 D.D. peripherally. At the point where each of the three ended, there ran an unmistakable choroidal vessel, each a direct continuation of a streak and in no way different in appearance from the many choroidal vessels lying side by side and easily seen in the lightly pigmented periphery.

The third feature, also reported by Klien and Holloway, was pigmentation of retinal vessels. The pigment, coarse and granular but of the same color as the streaks, had developed as elongated patches enveloping two small vessels, within ½ D.D. of each other, lying well out toward the periphery, beyond the ends of the streaks themselves.

The patient's general physical examination was negative except for irregular depressions of a linear character in the skin, rather resembling faint scars or the striae of pregnancy but without a trace of the lightly colored papules characteristic of pseudoxanthoma elasticum. Nevertheless, they may represent an early stage of pseudoxanthoma, though discovered by the patient 10 years before, because they showed the typical distribution in the cubital and popliteal spaces. They were, however, present also along the inner and anterior aspects of the arms and upper thighs, but absent from the neck and axillae.

Case 2.—J. M., a white woman of 64, in good general health, became aware of an abnormal skin condition involving the neck and axillae at the age of 23. Three years prior to my examination, when the lesions had spread to the cubital and popliteal spaces, as well as to the groin, the patient saw a dermatologist, who made the diagnosis of pseudoxanthoma elasticum. Three years before this, because of blurring in the left eye, she had consulted an ophthalmologist, who made a diagnosis of angioid streaks. At this time, vision was 20/30 in the right eye and 20/70 in the left eye with small plus cylinders for correction. Both fundi showed many radiating dark streaks and several small hemorrhages in the maculas. Three years prior to my examination vision was correctible to 20/70 in the right eye and to less than 20/200 in the left eye. Only a few faint streaks were then visible in each eye, against a background of advanced choroidal sclerosis in the posterior polar regions. Vision was the same when I first saw her, in May, 1953, and there was extensive choroidal sclerosis, accompanied by what seemed to be a total loss of pigment epithelium surrounding each disc for about 3 D.D. Beyond this the fundi were colored a light red, with faintly visible choroidal vessels, identical in appearance with normal lightly pigmented fundi. The more or less circular border between the normal-appearing and the depigmented zones was clearly defined and marked in places by a thin deposit of pigment. In the right eye, the macular

region was almost entirely white from the thick matting of sclerosed choroidal vessels, and there was a faint dusting of pigment. A single black angioid streak, about as wide as a retinal artery near the disc, was seen to emerge from under densely packed choroidal vessels about 1 D.D. from the disc at 6 o'clock and to proceed 3 D.D. inferiorly toward the periphery, tapering gradually as it did so and terminating with two or three sinuous turns, much like the corkscrew effect of macular arteriosclerosis. While early in its course it seemed to pass behind four or five choroidal vessels, toward its end it seemed to pass in front of several. In other words, as it traveled away from the disc, it appeared to become more anterior.

In the left eye, a similar angioid streak was made out, somewhat fainter, but nevertheless definitely outlined. First appearing from below a retinal artery, 1 D.D. nasal to the disc, it passed inferonasally and ended as a very thin sinuous black line about 3 D.D. from the disc. Again, there were several crossings above the streak of sclerosed choroidal vessels. Almost continuous with this streak, but fainter and broader, was another, which coursed concentrically with the disc, about 1 D.D. away, and at 11 o'clock struck out toward the periphery for about 3 D.D., where it disappeared at the border of the normal-appearing fundus. The left macula showed ill-defined, but dense, pigment accumulations, about ½ D.D. in size, against the white background of choroidal sclerosis.

COMMENT

That the nature of angioid streaks is still not well understood in spite of several pathologic reports is accepted by a number of recent authors.‖ Two of six pathologic studies made in well-authenticated cases have revealed no breaks in Bruch's membrane whatever. In addition, Friedenwald ¶ has stated that he was unable to find any pathologic basis for the clinical picture, and Reese,# examining sections from a case of Clay, concluded that anomalous vessels were responsible. Even assuming that tears in Bruch's membrane are present in the majority of cases, it must be shown that such tears are primary and causative. This has not been done.

One of the principal objections to Kofler's theory is the problem of explaining wide brown to black streaks in terms of tiny chance fissures in a minute membrane sandwiched, as it is, between two much thicker and blackly pigmented layers, which oftener than not remain intact over the breaks. The dimensions of these layers speak for themselves. According to Duke-Elder,[43] the lamina vitrea averages 2.5 μ in thickness, but the lamina elastica, or outer layer, which is the only one involved, measures 0.5 μ, as compared with the average height of pigment epithelium of 8 μ and an average thickness of the posterior choroid of 220 μ. In other words, we are asked to believe that the opacity of a normally clear membrane, one-sixteenth the width of a densely pigmented layer lying on top of it and one four-hundred-fortieth the thickness of a heavily pigmented layer lying behind it, can so materially affect the general appearance of the fundus that minute rents in it become visible as dark streaks sometimes five times the width of the largest retinal veins.

The dark color, so common in these cases, is also difficult to explain on the basis of tears in Bruch's membrane. Because of the exposed choroidal vessels, one would expect them to be invariably red, instead of brown or black. Neither Hagedoorn [40] nor Klien [15] has given the answer. Verhoeff [12] suggested that the pigment of the choroid would absorb the light, while the opaque membrane of Bruch would reflect it; but he failed to take into account the light-absorbing properties of the overlying pigment epithelium. One also wonders why a few crossing choroid vessels should

‖ References 3, 5, 8, 23, 42, and 75.

¶ Fridenwald, cited by Lewis and Clayton.[41]

Reese, cited by Wagener.[42]

often be clearly visible while the rest are lost to view. In a given fundus, where the pigmentation is uniform, one would expect all the vessels to be visible through the fissures in more or less the same degree.

Then, again, if it is true that interruptions in an opaque Bruch's membrane can give brown or black streaks, why should not one infer that in normal eyes, in which the membrane is not opaque, the fundi would be brown or black? Further, how does one reconcile the perfectly normal appearance of the areas between the streaks with opacity of the membrane?

Because of these, and many other, objections to Kofler's theory, to be dealt with at greater length later, I am suggesting one that seems less at loggerheads with the clinical picture. I believe that angioid streaks almost invariably bring to mind the idea of pigmented vessels because they are pigmented vessels and that they have gone so long pathologically unrecognized because they are vessels for the most part of normal size, course, and location; and, further, that this location, the choroid, is so densely pigmented under normal circumstances that an excess of pigment about certain choroidal vessels would be extremely difficult to pick up microscopically. Evidence for the last point may be had from the pathologists themselves. Samuels and Fuchs,[44] for example, stated that the ophthalmoscopic degree of pigmentation of the fundi is impossible to estimate exactly from histologic examination. Hagedoorn [40] wrote:

> A normal choroid, preserved in a solution of formaldehyde, appears collapsed, thin and strongly pigmented with flat, intensely staining nuclei, so that it requires careful examination to locate the arteries.

In this connection, it is interesting to note that in one of the two pathologic studies of unquestioned angioid streaks where there were no breaks in Bruch's membrane, Benedict [38] described the choroid as showing "perivascular lymphocytic infiltration about many of its vessels and heavy deposits of pigment surrounding the vessels and nerves. . . . There was perivascular lymphocytic infiltration in the episcleral vessels, most marked in the anterior sections, and a considerable amount of pigment about the vessels and nerves traversing the sclera."

If, then, the streaks are in fact excessively pigmented vessels in the choroid, it is not difficult to understand why pathologically they might well be overlooked.

I. Pigmented Choroidal Vessels(?)

A. Signs of Systemic Vascular Disease.—First, it cannot be too strongly emphasized that the fundus condition is commonly associated with a generalized vascular disorder, central or peripheral. As early as 1891, Plange,[17] whose publication on angioid streaks was preceded only by Doyne's, mentioned in his case a low radial pulse with flattening of the curve. From this he inferred a vascular loss of elasticity, which he surmised might be a factor of importance in the fundus hemorrhages. Scholz [2] noted the absence of vascular pulsations in the lower extremities of his third case. Guenther,[45] investigating pulse wave velocity and form in peripheral "musculoelastic" arteries, found abnormalities in nine cases of angioid streaks. He concluded that these were such as to indicate elastic tissue degeneration of the vessel walls. In 1946, Scheie and Freeman [46] found diminished or obliterated peripheral vascular pulsations in two of three cases of angioid streaks (the third had hypertension), confirmed by oscillometric studies. Biopsy of the ulnar artery in one case

revealed elastic tissue degeneration with a "compensatory" muscle tissue hypertrophy. X-rays revealed calcification of thigh vessels in two cases. A similar vascular calcification was found in Zentmayer's [5] case in the region of the sella turcica, "probably within the internal carotid artery," as well as in the peripheral arteries of a case of Silvers and Wolfe.[47] Dixon [48] reported a case with aneurysm of the intracranial portion of the internal carotid artery. Bock [39] described atheromatous changes in the aorta and degeneration of the posterior ciliary arteries. Klein [15] and Hagedoorn [40] regarded the choroidal vessels as sclerotic. Repeatedly one finds described in the literature choroidal sclerosis in these cases. Wildi [49] observed the development of six small aneurysms in the macular arterioles of one case. Even in pseudoxanthoma elasticum small hemorrhages have been found in the skin lesions.[32] Already mentioned is the 23.3% incidence of generalized vascular disease in the 60 cases reviewed by Holloway.[11] One can only speculate on the number of cases in which the vascular disorder has gone unrecognized. That it plays an important role is reflected by the decreasing incidence of angioid streaks in patients beyond their 50's. This has been interpreted as the result either of a shortened life span in these cases or of absorption of the streaks. The latter supposition seems less likely in view of the figures Scholz has given on cases followed for more than a year. It will be remembered that of 46 such cases, 33% showed an increase in number, 56% no change, and 10% a decrease.

B. Signs of Local Vascular Disease.—While the pathogenesis of the two other systemic disorders, Paget's disease and pseudoxanthoma elasticum, is not sufficiently well understood to throw any light upon the question as to whether choroidal vessel pathology is responsible for the streaks, the associated fundus lesions very decidedly point in this direction. There is not one lesion which cannot be explained as the result either of choroidal hemorrhages with secondary pigment disturbance or of a deficient choroidal circulation. Many of these features allow no other interpretation.

1. Hemorrhages: The development of hemorrhages, either spontaneously or after slight trauma, in such a high percentage of cases is in itself good evidence of the circulatory nature of the disease. It is a curious fact that the peculiar form taken by these hemorrhages in so many cases has escaped comment. Over and over they are described as linear, like the pigmented streaks themselves, and sometimes several disc diameters in length. Apparently because of this resemblance, de Schweinitz [10] thought that the streaks were "metamorphosed" hemorrhages. Despite their shape, which, of course, is characteristic of hemorrhages in the retinal nerve fiber layer, few doubt that they are in the choroid. In my first case, not only were they linear and, except for color, identical with the dark streaks, but also, in two places, they were direct extensions of the streaks. Similar hemorrhagic continuations of angioid streaks have been reported by others.* Since red intervals in dark angioid streaks are most commonly due to exposed underlying choroidal vessels, many of the later writers have concluded that this is invariably so and that earlier observers, reporting hemorrhages, have confused the one with the other. In my own case, their gradual absorption along with the larger hemorrhagic masses left no doubt as to their origin. In most instances, however, the linear hemorrhages have been described as independent of the streaks. Bedell in his fourth case found three linear hemor-

* References 10 and 20.

rhages, "one a narrow line, fairly sharp and distinct." In Clay's third case, immediately surrounding each disc was a "narrow ring of hemorrhage." Calhoun [50] wrote, "On each side and below the macular changes were long extravasations of blood which appeared to be in the outer retinal layers." The accompanying illustration reveals three separate linear hemorrhages. Holloway [11] noted in one case "a delicate hemorrhagic streak," and in another, "an elongated narrow crescentic hemorrhage." Goar [51] wrote that continuous with a large flat hemorrhage in the macular region "was a finger-like process extending nasally and connecting with a large extravasation below the disc. There were two small linear hemorrhages nasal to the disc." In 1895 Holden [52] observed that "as the hemorrhage became further absorbed a narrow process of red color pushed upward from its superior margin and gradually extended a distance of 2 D.D. in a curved streak, but slightly broader than a vein on the disc." Jones, Alden, and Bishop,[12] in an article on pseudoxanthoma elasticum, referred to "flame-like" hemorrhages in their third case. Bedell,[8] Clay,[9] and Coppez and Danis [6] mentioned linear hemorrhage surrounding angioid streaks.

Emphasis is placed upon this finding because hemorrhages of this shape and location occur in no other condition and because they point to a peculiar disease of the vessel walls which leads to extravasations of blood along considerable portions of their length rather than at isolated points of weakness, as in the usual types of vascular disorder. If one assumed that early in the disease the extravasations were serous, rather than hemorrhagic, as in juvenile disciform degeneration of the macula, and that the pigment epithelium reacted by migrating about the affected vessels, one could better understand how in some cases the streaks could develop without any prior hemorrhages. It might also explain the tendency of the hemorrhages, when they do occur, to form in relation to the streaks, for the vessels developing transudates would naturally be those which, under greater stress, would most likely show outspoken hemorrhage. In any event, Batten,[7] apparently entirely unaware of the tendency to linear hemorrhage formation, concluded:

> The causation of these cases is best explained, clinically, by assuming that there is a slow form of oozing, or seepage, from the choroidal vessels, without gross hemorrhages, but allowing the blood to percolate through the vessel walls along the course of the choroidal vessels, giving rise to the angioid streaks, and that the same vascular weakness would account for the various forms of retinal and choroidal disturbance of pigment, found in this disease.

How much more convincing this explanation becomes in view of the frequency of linear hemorrhage. Yet Batten based his conclusion upon entirely different considerations, namely, the high incidence of generalized vascular disease, the predisposition to choroidal hemorrhage, and the large number of patients with siblings who showed the associated fundus changes without the streaks themselves.

2. Macular Pathology: Another common associated finding in cases of angioid streaks, no less important than choroidal hemorrhages as evidence of the fundamentally vascular nature of the disease, is the presence of macular pathology. Edema, exudate, or hemorrhage, individually or in any combination, usually characterizes the early stages of the macular disease. After a few months this may subside, with return of normal vision, or permanent impairment may result from scar tissue. Whatever the course, the significant feature of the lesions is that they may occur without angioid streaks even approaching the macula. Indeed, they are found before the streaks develop anywhere in the fundi and may, in fact, never be followed by the

development of streaks in the siblings of persons with typical streaks.† Butler's [53] patient was first seen because of metamorphopsia. No fundus pathology was found. Vision was 6/6 in the right eye and 6/12 in the left eye. One month later, when, unfortunately, an ophthalmoscopic examination was not done, it was 6/30 in the right eye and 6/24 in the left eye. Six months later, vision was 6/60 in the right eye, and characteristic angioid streaks were found in both eyes, with a soft white exudate in the right macula. Four months after this, vision was 1/60 in the right eye and 6/12 in the left eye. At this time the macular exudate had shown marked contraction and the streaks had become much less evident. Hibbert's [54] case resembled Butler's in that macular and other scattered exudates with visual disturbance preceded the development of the streaks by more than a year. Butler stated emphatically that streaks were not present in his case on first examination. From reading Hibbert's paper, it is not entirely clear whether they were absent or simply not recognized during the first year of observation. In any event, how the theory of the streaks as tears in Bruch's membrane, injuring the choriocapillaris and so producing hemorrhage, can be made to explain macular exudates, under any circumstances, or even explain hemorrhage, when no streaks are in the neighborhood or when they are absent altogether, is difficult to understand.

In the later stages of the macular disease, a disciform degeneration, indistinguishable from the senile type, frequently appears. Verhoeff and Sisson [55] rejected Behr's theory that tears in the membrane of Bruch were responsible for senile and juvenile disciform degeneration and, like most authorities today,[43] attributed the latter to a disturbance in the choroidal circulation. In support of this, they argued that the association of disciform degeneration with angioid streaks was in accord with their conclusion, "for choroidal hemorrhages are frequent in cases of the latter condition and indicative of vascular disturbances which might well lead to hemorrhage or serous exudations from the choriocapillaris behind the macula." In other words, they felt in 1926 that the changes in Bruch's membrane were secondary to choroidal extravasations, while now Verhoeff regards them as primary, if not in the senile and juvenile forms of disciform degeneration, at least in angioid streaks.

3. Connective Tissue Formation, Resembling Retinitis Proliferans ‡: The scar tissue often seen in the terminal stage of the macular lesion, the evolution of which was followed in my first case, is similar to the white lines accompanying the streaks on one or both sides. In more recent years adherents of the Kofler theory have interpreted the latter as connective tissue forming along the edges of the membrane defects, an explanation which seems unconvincing, for two reasons. First, in tears which occur in other conditions, such as myopia or choroidal ruptures, the connective tissue fills in the gap, producing a white streak rather than lining its edges, and the result bears no clinical resemblance to dark angioid streaks. Second, the lines sometimes extend beyond the streaks as a kind of tail, or may rise somewhat above the surface of the retina, as in retinitis proliferans. Further, when they border the streaks, they give a sheathing effect. In short, their appearance is of a kind that in every other condition results from vascular extravasations. They even tend to appear oftener about the streaks in the macular areas, as in the first case described.

† References 7, 50, and 62.

‡ References 17, 42, 56, 57, and 59.

where such extravasations are most apt to occur. Similar sheathing in other disorders is known to develop in association with the choroidal vessels and is illustrated in Troncoso's text.[58]

4. Miscellaneous Associated Fundus Lesions (Choroidal and Circumpapillary Atrophy, Pigment Stippling, Drusen, and Exudates): These are changes which without exception one customarily associates with circulatory disorders in the choroid. Circular atrophic areas, usually but not always, located in the course of the streaks, were seen by Doyne [16] to form as hemorrhage was absorbed. Holden,[59] Zentmayer,[5] Clay,[3] and Collins [1] agreed upon their probable hemorrhagic origin. Indeed, their association with the streaks in so many instances argues for the vascular nature of the streaks, while their occasional occurrence alone is additional evidence that the streaks, or tears in Bruch's membrane, are not essential to their development, as the theory of mechanical injury to the choriocapillaris demands. That all the other associated changes may, in fact usually do, exist at a distance from the streaks has, of course, the same significance.

Circumpapillary atrophy when present seems to take two forms. It may be an actual chorioretinal atrophy, indistinguishable from the senile type, or it may consist of an overgrowth of glial tissue, sometimes disappearing after many years, as in Zentmayer's case.[5] The atrophic form seems the commoner of the two and may well arise from a deficiency of the choroidal circulation in much the same way as "halo senilis."

Pigment stippling or flaking, on the other hand, seems to appear in no other condition. Most authorities look upon it as a disturbance in the pigment epithelium. Collins [1] and Magitot § attributed it to the pigmentation of the fine punctate hemorrhages often reported in much the same locations.‖ The presence of these hemorrhages in the periphery away from the streaks is, again, striking evidence of the independence of the vascular disorder so far as the streaks or membrane tears are concerned. Interestingly, the flaking may be found with white spots in the periphery, presenting a picture very similar to the so-called "pepper and salt" fundus, a condition which, of course, is primarily vascular.

Drusen of two types, those originating from the pigment epithelium and those found in the nerve head, are common. The former, at least, indicate the presence of either vascular disease or a heredodegenerative process,[60] and so their high incidence in these cases may be taken to support the idea of either a primarily choroidal vascular disease [49] or a basic degeneration of Bruch's membrane.[61]

The presence of exudates, on the other hand, especially those which develop and disappear rapidly, as in the cases of Butler [53] and Hibbert,[54] are, to say the least, difficult to reconcile with a primarily degenerative process.

5. Associated Fundus Lesions Without Streaks in Siblings of Typical Cases: Many authors have noted the high incidence of nonspecific chorioretinal disease, as well as cardiovascular-renal disease in siblings ¶ of patients with typical angioid streaks. When these siblings, in whom the streaks never develop, are considered along with those cases in which they appear after the associated fundus lesions,

§ Magitot, cited by Holloway.[11]

‖ References 1, 3, 7, 15, and 75.

¶ References 7, 50, and 62.

sometimes years later,# one gains the impression, as Batten emphasized, that streak formation is not essential to the clinical picture. It was for this reason that Batten believed the streaks to be simply one among many manifestations of an underlying choroidal vascular disorder, any one or a combination of which could be missing. The *sine qua non* of the condition was, in his opinion, the choroidal disease. Lloyd * referred to three sisters whom he had examined—one with bilateral macular degeneration and typical angioid streaks, another with all of this in one eye and macular degeneration without the streaks in the other, and the third with only slight bilateral macular changes.

Nonspecific chorioretinal disturbances without angioid streaks are also found in cases of pseudoxanthoma elasticum. Benedict and Montgomery [63] reported eight cases of the skin disease. Of five in which the eyes had been examined ophthalmoscopically, two showed typical streaks and the other three various forms of chorioretinal disturbance only.

C. The Streaks Themselves—"Angioid" Characteristics.—1. Resemblance to Choroidal Circulation: If none of these changes so often seen with angioid streaks, these signs of choroidal extravasation or circulatory deficiency, existed and nothing at all were known of the generalized vascular disease so common in these cases, one would still be tempted to regard the streaks as basically vascular because of their own special characteristics. Their radial distribution, with the branching and anastomosing, remind one irresistibly of the choroidal circulation, particularly when it is seen in subalbinotic and the lightly pigmented fundi of myopes. To appreciate the likeness fully, one must see beyond the choriocapillaris layer, which is not possible in so many cases of choroidal sclerosis. Collins [1] has emphasized the importance of this resemblance and pointed out that it may be better appreciated in the fundi of certain monkeys. The marked difference in caliber of adjacent choroidal vessels, the tendency for some vessels to turn and partly circle the disc, the denser anastomotic network near the discs, often forming an incomplete circle, and their origin near, but not at, the disc margins—all these correspond to the characteristics of the streaks. Even the peculiar tendency of the streaks to terminate before reaching the equator, commented upon by a number of authors,† may, as Collins remarked, bear some relationship to the distribution of the posterior ciliary arteries, supplying, as they do, the posterior half of the choroid. Another puzzling feature, the frequency of a peripapillary pigment ring, which occurs oftener than the occasional findings of this configuration of the choroidal vessels near the disc can justify, may be explained, as Collins wrote, by pigmentation of the circle of Zinn, for there is no reason why this structure should not become as visible in this way as the choroidal vessels themselves, lying, as it does, not far from the inner scleral surface. The seeming denseness of the network near the discs could be simply the result of vessels crossing one another, rather than actually joining, as Calhoun remarked.[60]

2. Tapering: Several other characteristics of the streaks put one in mind of vessels. For one thing, tapering as the streaks approach the periphery is hard to explain on any other basis. It was especially noticeable in the second case presented

References 11, 53, and 54. Reese, cited by Zentmayer.[3]

* Lloyd, in discussion on Bedell.[8]

† References 20, 41, 50, 64, 65, and 75.

and has been reported often in the literature.‡ It seems significant that tapering in the reverse direction, that is, centrally, has never been reported.

3. Ampulliform Dilatations: Marked dilatations of the streaks, usually about the disc, and often termed "ampulliform," or "sinus-like," have been repeatedly noted.§ Whether there is any connection between these and actual aneurysms is, of course, conjectural, but one cannot help remembering the carotid aneurysm in Dixon's case [48] and the tiny aneurysms of the macular arterioles in Wildi's case.[49] One recalls, also, that Salzmann [69] wrote:

> Abnormal vortices have occasionally been observed in myopic eyes at the border of the choroidal foramen, more rarely in eyes of normal form.

4. Variations in Depth: On the strength of the foregoing characteristics alone, one would be entitled to think of the streaks as vessel-like, or "angioid"; but, in addition, there is the observation that the streaks do not lie on a single plane. They often seem to cross above the choroidal vessels in some places and to pass below them in others. This was evident in both cases presented, was confirmed by another ophthalmologist, and may be seen in Figure 2. No other author has referred to this finding, although Calhoun [50] wrote (and Clay [3] apparently concurred in the opinion) that in his case "some of the streaks appear to be at different levels and some are denser, and besides one may imagine the color to be darker where two streaks cross." Hughes [70] saw crossing choroidal vessels which were part of a barely visible choroidal vessel pattern lying on each side of the streaks but assumed that the vessels were deep to the streaks. Inasmuch as he thought that the streaks were caused by tears in Bruch's membrane which had become brown or black through the accumulation of pigment, it must have been difficult for him to understand why the choroidal vessels became clearer and a brighter red when they crossed under the streaks than when they were in the adjacent normal fundus. Even accepting the current view that the defects are not filled with pigment and become visible only through exposing the choroid, one wonders why just a few vessels are seen at scattered points and the rest are lost to view in choroidal pigment. There is, however, nothing puzzling about this if one pictures the visibly crossing choroidal vessels as lying anterior to the streaks, while the rest lie behind.

That the streaks occupy a level deeper than Bruch's membrane is also suggested by their disappearance in areas of choroidal hemorrhage, as seen in Figure 1 and described by Wassenaar [24] and others.

5. Color Variations: Many writers mention the way in which brown streaks become red for varying distances. Most authorities ascribe the red to the underlying choriocapillaris or larger choroidal vessels which cross the streaks, but careful study of the large vertical streak below the left disc in Figures 2 and 3, as well as reports in the literature, makes it seem likely that often a single choroidal vessel is being exposed within the streak, not a densely packed mass. One gets the impression in my case that the vertical brown streak, enclosing the red, follows every twist and turn of the latter. Also, the central red band can be traced for short distances in the normal fundus and seems to be a part of the general choroidal vessel pattern. It is

‡ References 1, 2, 5, 17, 20, 23, 49, 66, 67, and 70.

§ References 1, 3, 6, 7, 8, 23, and 68.

easier to think of the red portion as a vessel lined on each side by pigment and exposed anteriorly by a thinning of the overlying pigment epithelium than as a mass of random, crossing vessels from which no individual vessel can be differentiated. This impression has been gained by several observers.‖

The white portions of the streaks, as opposed to bordering sheaths, are thought to be sclera revealed by choroidal and pigment epithelial atrophy. As already mentioned, a very similar degeneration is seen in choroidal vessel disease.

Both Leber¶ and Holm[71] agreed that no better evidence is afforded for the vascular and pigmented nature of the streaks than their color variations.

6. Evidence of Pigmentation: Although, as Calhoun[50] wrote: "The resemblance of the streaks to the arrangement of the choroidal vessels has long been noted," objections are raised to identifying the two, for several reasons. First, how can one explain the absence of substantiating pathologic findings? The answer to this has already been suggested. Second, if the streaks are vessels, why are the edges irregular, even serrated, and not smooth. Third, how could there be such great variations in width along the course of one vessel? As Wassenaar[23] pointed out, both these characteristics might easily be due to irregularities in the deposition of pigment. Fourth, how do the choroidal vessels become visible through an intact pigment epithelium? Again, pathologic pigmentation would seem to be the cause, in much the same way as it serves to bring out the vessels in cases of Siegrist's dots.

What other evidence do we have for the role that pigment plays in streak formation? Of course, the fact that the major changes in the fundi, apart from the streaks themselves and the hemorrhages, are caused by pigment disturbance, often of a very peculiar sort, such as the stippling, for example, may be significant. When one sees massive accumulations of dark-brown pigment and flaking of exactly the same color as the streaks, it is difficult indeed to think of the streaks as other than pigmentary. Then, of course, there was the observation, in the first case presented, of three parallel streaks which changed abruptly from brownish black to red about 3 D.D. from the disc and continued toward the periphery as unquestionable choroidal vessels, in no way different from those lying on each side. Several of the older writers have mentioned the same finding.# Finally, the occasional migration of pigment about the retinal vessels in these cases would seem to support the idea of a similar migration to the choroidal vessels. It will be remembered that in my first case elongated deposits of pigment had formed about two small peripheral retinal vessels. Klien[15] wrote in reference to her second case: "One retinal vessel, crossing a large streak, was at first observed to have a sheathing with a greyish black pigment. This disappeared in the course of several months." Holloway[11] observed the grouping of pigment about the terminal branches of macular vessels. Many writers have seen pigment of the Siegrist type form along red angioid streaks.* According to Collins,[1] Lindner "noted that in three of his eight cases the streaks were not continuous but consisted of a series of dots arranged somewhat in correspondence with the choroidal vessels." Holm[71] followed the development of

‖ References 11 and 20. Coats, cited by Holloway.[11]

¶ Leber, cited by Holm.[71]

References 11, 23, and 71.

* References 3, 8, 20, and 23.

a typical case of angioid streaks from an early stage in which they bore a striking resemblance to Siegrist's dots. When the condition was fully developed, he wrote of this case: "The vessels which formed the continuation of the pigmented areas presented all the typical criteria of choroidal vessels so as to leave no doubt in the observer."

Pathologically, pigmented streaks have been demonstrated over sclerosed choroidal vessels in conditions unrelated to angioid streaks by Lindner,† Siegrist,[72] and Bayer.‡ A. Fuchs [73] reported finding obliterated choroidal arteries with a covering of pigment epithelium.

Whether pigment enters into the composition of the streaks or not, it is interesting to note that even those authors who question the possibility fall into the habit of referring to them as pigmented because of their ophthalmoscopic appearance.§

I. Tears in Bruch's Membrane(?)

A. Poor Correlation of Streaks with Associated Fundus Lesions.—Many of the arguments brought in support of the pigmented choroidal vessel theory serve as well to refute the Kofler hypothesis. The frequent occurrence of all the associated lesions independently of the streaks, whether in other parts of typically affected fundi, in fundi of cases in which streaks develop perhaps years later, or in fundi of siblings who never develop them, is an example. Further, some of these lesions, like transient exudates and linear hemorrhages, are of a type that simply cannot be explained on the basis of tears in Bruch's membrane with mechanical injury to the choriocapillaris. Not only may the associated lesions precede the streaks by many years, but, conversely, the streaks may be observed for many years without any other pathologic changes in the fundi.‖ When the associated lesions do appear, the streaks themselves may remain entirely unaltered.

B. Poor Correlation of Streaks with Membrane Tears.—The question of how tears become visible in a minute membrane lying under an intact densely pigmented layer, 16 times as thick, has already been raised. If, however, these tears were found pathologically to coincide with the position of the streaks, one might still give the Kofler theory serious consideration; but in fact they do not.¶ It is a common thing to learn that few streaks were seen clinically whereas pathologically numerous breaks were found in the membrane.# A rather complicated discussion by Hagedoorn [40] of how he reconstructed the outlines of a membrane tear by following it in serial sections, thereby showing its resemblance in form to a typical streak, has led to the mistaken impression on the part of at least two authors * that he had succeeded in correlating the positions of the tears with those of the streaks. But this has not yet been done. Nor has anybody described a tendency on the part of the tears to anastomose. Instead, one gets the impression from the pathologic reports that the tears are often random and isolated, unlike the streaks, which always com-

† Cited by Verhoeff, in discussion on Bedell.[8]
‡ Bayer, cited by Scholz.[2]
§ References 5, 8, and 65.
‖ References 8, 12, 23, and 39.
¶ References 42 and 75.
# References 15 and 40.
* References 2 and 5.

municate with each other. To make matters worse, the breaks may be artifacts,† the result of sectioning, and as such are difficult, if not impossible, to differentiate from those which existed in vivo.

C. Membrane Tears Without Streaks.—Tears in Bruch's membrane are not uncommon, nor are they peculiar to the condition of angioid streaks. They may appear in such unrelated conditions as disciform degeneration, juvenile or senile; myopia; traumatic choroidal tears; albuminuric retinitis; choroidal sclerosis, and, most important, in many senile cases accompanied by basophilia of the membrane. Verhoeff and Sisson [55] found basophilia and tears "essentially identical" with those in Hagedoorn's case of angioid streaks in 70 of 600 cases chosen at random and concluded that the condition was simply a senile manifestation without any special pathologic significance. Scholz [2] mentioned that 10% of 200 cases at The Johns Hopkins Hospital showed intense basophilia. These pathologic examinations were presumably done on eyes that were normal, inasmuch as ophthalmoscopic examinations were often lacking. If eyes had been deliberately chosen with local (especially choroidal) circulatory disturbances, it is probable that these changes in Bruch's membrane would have been discovered in a much higher percentage of cases.

On the one hand, then, we have evidence that tears in Bruch's membrane often occur without angioid streaks, while, on the other, at least two pathologic studies on well-authenticated cases demonstrate that streaks may exist without tears.

D. Variations in Streak Width—an Elastic Component?—In order to account for the breadth of the streaks and such complications as hemorrhages, many supporters of Kofler's theory have found it necessary to assume an elastic component. A few thought this was furnished by Bruch's membrane, but the idea was later abandoned when it was realized that the membrane was not only degenerated but also calcified. Verhoeff [12] then suggested that the choroid was the source of the elasticity which widened the defects. He argued that in the senile cases with ruptures in the membrane but without streaks the choroid was sclerotic and inelastic, so that the breaks were narrow with overriding edges and therefore not visible as streaks. Such an explanation might apply if, in cases of angioid streaks, defects in the choroid corresponded with those in the membrane, but since they rarely do, and in fact may be altogether absent, it is impossible to understand how the choroid could exert any traction.

To assume that tension from any source is a factor in the production of streaks poses many questions. The complicated mosaic pattern of the streaks in so many cases would result in the release of tension in the more central areas, so that if the streaks could form at all, according to this principle, they must necessarily form first centrally, then peripherally, a sequence never described in the literature. Then, too, how does one account for the large variations in the width of a single streak, the tendency to taper toward the periphery, the absence of widening at streak intersections,[23] and the presence of radial streaks when the tears which occur on contusion of the globe are characteristically concentric with the disc?

E. Miscellaneous Questions.—Why is Bruch's membrane the only elastic membrane in the eye which is involved in the degeneration, and why, particularly, is its

†References 15 and 40.

posterior portion, as indicated by the presence of the streaks, posterior to the equator? Does this not point to some relationship between the degeneration and the choroidal circulation?

What causes the streaks to fade, to become thinner, or to disappear altogether,‡ without a trace of scar tissue, sometimes in a matter of months, when it is generally acknowledged that the breaks in Bruch's membrane are never repaired?

How does one explain the crossing by brown or black streaks of white areas of choroidal atrophy where no pigment remains§ or of white areas of choroidal sclerosis, as in the second case presented, if the streaks are nothing more than fissures in an opaque membrane? Finally, in the same case, how can one account for the visibility of the sclerotic choroidal vessels, seen in every detail, if the membrane of Bruch is opaque?

SUMMARY

The nature and origin of angioid streaks are still unsettled questions. That a systemic elastic tissue degeneration produces generalized vascular disease, as well as skin and eye lesions, seems probable. Whether the fundus pathology results from a primary degeneration of the membrane of Bruch with secondary choroidal changes or from a primary vascular disorder in the choroid leading to secondary and incidental ruptures in the membrane, bearing no ophthalmoscopic relationship to the streaks, is considered at some length. The weight of the clinical evidence seems to favor the latter view. A weakness of the choroidal circulation with, at first, serous and, later, hemorrhagic extravasations, usually accompanied by migration of pigment epithelium to the affected vessels, would seem best to account for the streaks, as well as the associated fundus pathology. A choroidal circulatory disturbance of this sort, then, becomes merely the local expression of a generalized vascular disease. Pathologic proof is lacking, but the difficulties of microscopic confirmation are indicated. Finally, no other theory seems as tenable. The tear-in-membrane hypothesis is incompatible with the clinical picture, and pathologic studies, when not contradictory, have been inconclusive.

543 Franklin St.

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SOME ASPECTS OF TORSION

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TORSION has been described by Donders [1] in 1847, by Listing [2] in 1854 and by Duke-Elder [3] and many others; yet the subject of torsion remains unclear.

Of the two types, false and real, false torsion has become a controversial subject. In its demonstration, the projection obliquely of after-images on a flat wall caused distortion, a phenomenon which was finally explained by Le Conte [4] in 1881. Donders' and Listing's laws do not permit actual turning about the anteroposterior axis of the eye in moving from a primary position obliquely to a tertiary position, but Márques [5] quotes Helmholtz as believing that such turning does occur. Davson [6] feels the terms rolling, or real, torsion and false torsion can be used indifferently. Duke-Elder [3] draws a clear distinction between them.

The present paper is an attempt to clarify the picture. It consists, first, of a description of false torsion, and, second, it describes a simple method of observing real torsion objectively.

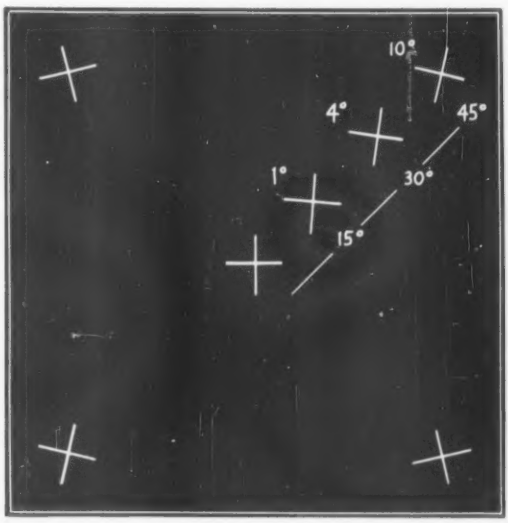


Fig. 1—Torsion of after-images, projected on concave spherical surface.

From the Department of Ophthalmology, Reading Hospital.

Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, Oct. 22, 1953.

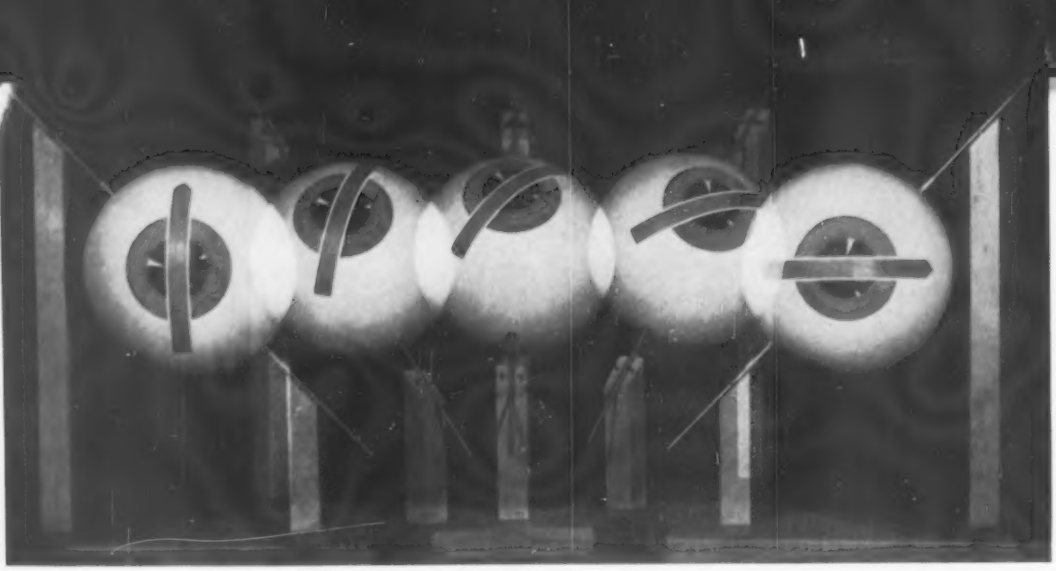


Fig. 2.—Composite photograph showing model of a left eye rotating around axis 45 degrees from the vertical. As the eye rotates, the camera is moved around the model. In the middle picture the camera is situated to the right of the stand. In the last picture the camera is behind the stand, and the eye, having rotated through 180 degrees, is looking directly backward. The vertical meridian of the cornea has undergone 90 degrees of torsion and has become horizontal.

FALSE TORSION

It is universally agreed that when the normal eye moves obliquely from a primary to a tertiary position, the vertical meridian of the cornea tilts. The end of the vertical corneal meridian which is nearest the original primary position is always tilted slightly toward the original primary position. Maddox [7] calculated the amount of this tilt. When the eye is rotated obliquely 15 degrees in the 45-degree direction, the tilt is 1°, when rotated 30 degrees it is 4° 6′, and at 45 degrees the tilt is nearly 10° (Fig. 1).

This is false torsion. It can be seen objectively by separating the lids widely and using as a line of reference on the eyeball an imaginary line from 12 to 6 o'clock, marked by a conjunctival vessel above, the pupil in the middle, and a vessel below. Torsion then becomes noticeable when the eye is made to rotate in an oblique cardinal direction. The larger the area of the eyeball exposed, the easier it is to see torsion.

There is nothing unusual about false torsion. It occurs when the eyeball or any other sphere revolves around an oblique axis (Fig. 2). Suppose the left eye is to revolve about an axis 45 degrees from the vertical. As the cornea begins to move upward and outward, the vertical corneal meridian begins to undergo apparent extorsion. If the rotation of the eye could continue through 180 degrees, until the eye looked directly backward, the vertical corneal meridian would undergo 90 degrees of extorsion and become horizontal.

It must have been thousands of years ago that the mind began to see objects in terms of vertical and horizontal lines—the dimensions of a room or the horizon. We are still using this planar coordinate system of vertical and horizontal lines to orient the surface markings of a rotating sphere, like the eye. We use the horizontal and vertical lines as references against which to judge the presence of torsion. Compared with these lines, the corneal meridians do tilt, and the amount of this tilt can be calculated in advance by trigonometry; but this tilt and these calculations are only measurements of the amount by which a planar coordinate system does not fit a spherical situation. False torsion is a consequence of using the planar coordinate system (Fig. 3*A*).

To observe accurately rotations of the eyeball, we must surround the eye with a spherical system of coordinates. All observations and measurements should be made in accordance with this spherical system. False torsion would then not exist. The ribs of an umbrella are an example of a spherical coordinate system.

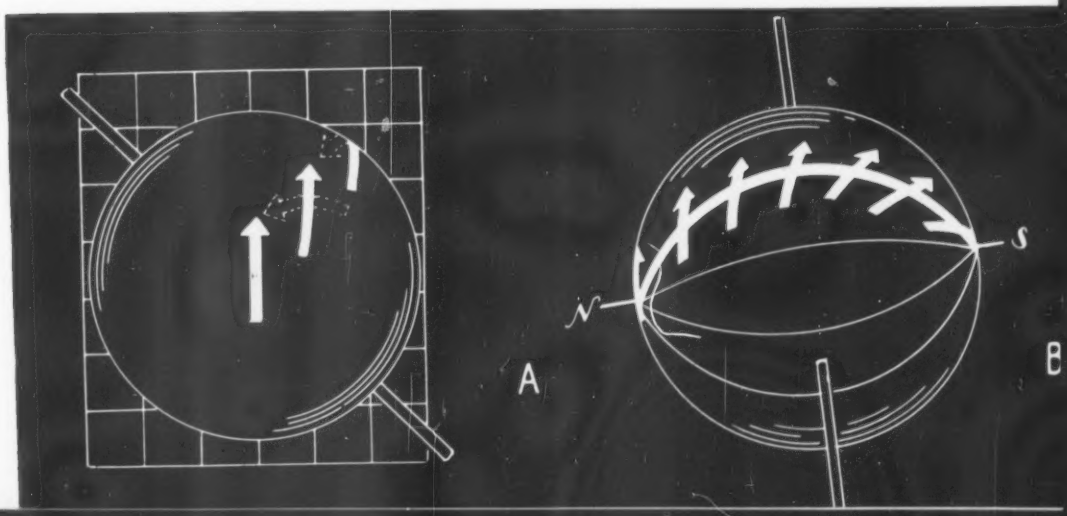
The perimeter uses a spherical coordinate system. If one produces a vertical after-image and projects it on a wall, false torsion will appear when the eye is moved in oblique directions; but if the after-image is made to move along the arc of a perimeter set obliquely, using the edge of the perimeter arm as a reference line, even though the image tilts, it will maintain a constant angle with the perimeter edge, showing that judged by the spherical coordinate system there is no false torsion.

The lines of longitude and latitude on a globe map of the earth are a spherical coordinate system (Fig. 3*B*).

When we look for torsion, this system should be made in the imagination to surround the eye in such a way that the globe map is turned on its side and the north pole coincides with the primary position in front, the south pole with the posterior pole of the eye. No matter in which direction the normal eye is then made to rotate, the vertical and horizontal corneal meridians will maintain a constant angle with the meridian of longitude along which the cornea is traveling. When the eye is viewed through this system of coordinates, there will be no false torsion of the eyeball even though the vertical meridian of the cornea becomes horizontal after it has rotated through 180 degrees (Figs. 4 to 8). Any real torsion of the eyeball around its antero-posterior axis immediately results in a change of the angle between the corneal meridians and the line of longitude along which the cornea is moving.

It is easy to view rotations of the eye through an imaginary spherical coordinate system (Fig. 9*A*). If the circular line of longitude along which we intend to rotate the eye, and will therefore use as a reference line to detect real torsion, is viewed on edge, it will appear as a straight line (Fig. 9*B*). If we sight along this 45-degree meridian, for example, it now appears as a straight line running in the direction of rotation of the eye. When this line is compared with a coincident imaginary line from a conjunctival vessel to the center of the pupil, any slight torsion of the eyeball can be detected. This will be real torsion, for false torsion is entirely eliminated from the picture. Real torsion is usually slight in amount, and it would be impossible to recognize it if false torsion were not eliminated in this way.

Fig. 3.—*A*, planar coordinates, behind sphere; *B*, spherical coordinates.



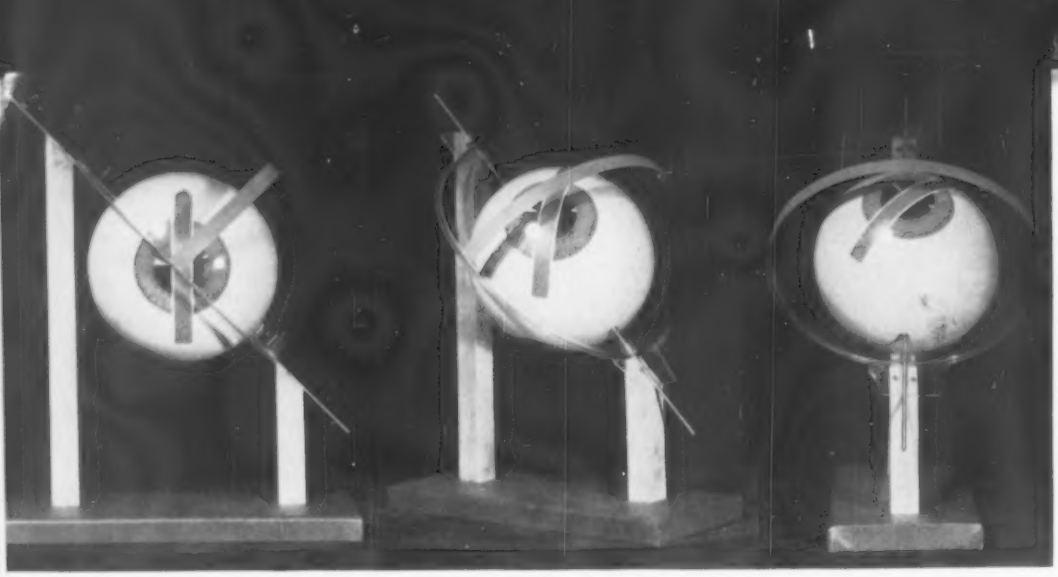


Fig. 4 (left).—A transparent plastic hemisphere has been placed over the model eye. On the surface of the sphere has been painted the 45-degree meridian of longitude. This painted line actually represents the edge of a plane which passes through the center of rotation of the eye and forms an angle of 45 degrees with the horizontal plane. The vertical corneal meridian forms an angle of 45 degrees with this 45-degree meridian of longitude.

Fig. 5 (middle).—The eye has begun to rotate upward and outward. The camera has been moved from the front to the side of the stand. The vertical corneal meridian has begun to tilt clockwise, but it still maintains an angle of 45 degrees with the 45-degree meridian of longitude, along which it travels.

Fig. 6 (right).—The left eye has now rotated upward and outward 90 degrees. The vertical corneal meridian has undergone clockwise rotation, or false torsion, of 45 degrees if judged by the planar coordinate system. When judged by the spherical coordinate system, however, no torsion has occurred, for the cornea maintains the same angle (45 degrees) with the 45-degree meridian as before rotation began.

The absence of false torsion when sighting along this oblique meridian of the direction of rotation proves that false torsion does exist when the eye is viewed against the conventional planar coordinate system. If the eye were not undergoing false torsion, that is, if the extraocular muscles were neutralizing it, then in this meridian, which does not show the false torsion, there would appear real torsion, produced by the corrective action of the extraocular muscles.

OBJECTIVE DETECTION OF REAL TORSION

The objective detection of torsion is difficult and requires practice, but so does the recognition of small amounts of heterophoria by the cover test.

In order to see small amounts of torsion objectively, the lids should be separated widely, exposing a large area of the eyeball; the opposite eye should be covered. With use of a bright light, a conjunctival vessel is selected such that an imaginary line from it to the center of the pupil coincides exactly with the proposed direction of rotation. If the eye is made to rotate precisely along this imaginary line and if the observer sights along this line, in line with it and the center of the eye, very small amounts of real torsion can be detected, even though they may occur only far out into the field of fixation.

The smallest amount of muscle weakness in which I have been able to detect torsion objectively occurred in a patient with paresis of the left superior rectus causing 4 degrees (8 $\triangle$) of right hypertropia in eyes up and left. In this direction of gaze with the right eye covered, slight extorsion of the left cornea could be detected, as though the left inferior oblique were helping to raise the left eye. There was the same amount of extorsion in eyes up and right. This observation of extorsion

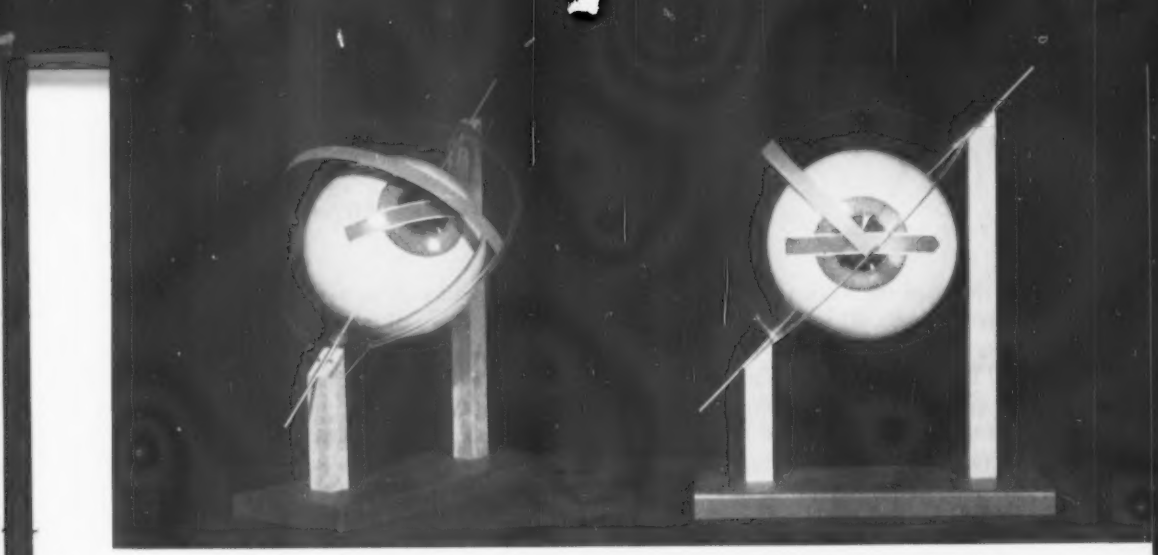


Fig. 7 (left).—The eye has rotated through about 160 degrees. The vertical corneal meridian has become almost horizontal, judged by the planar coordinate system, but still maintains a constant angle with the meridian along which it moves.

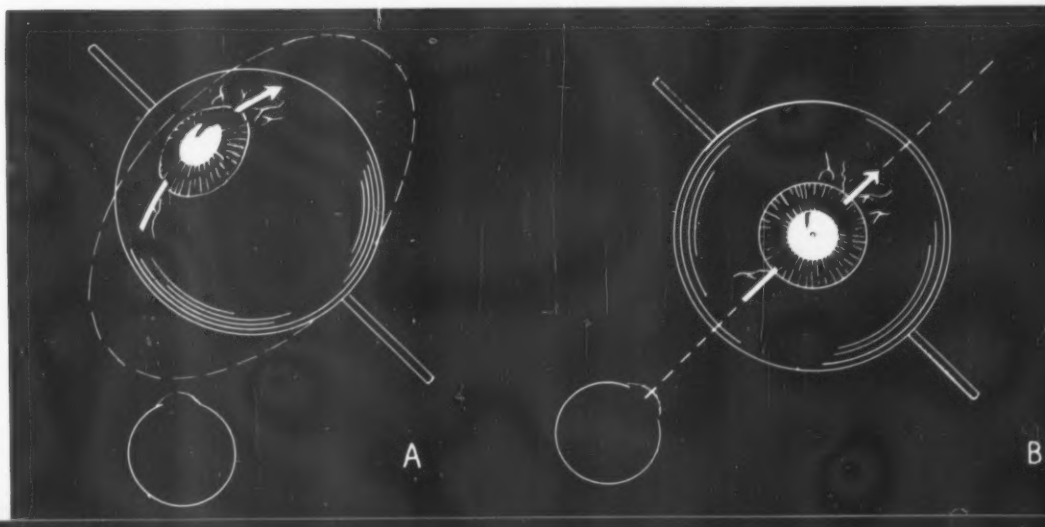
Fig. 8 (right).—The eye is now looking backward. The cornea has undergone 90 degrees of false torsion according to the planar coordinate system. Since it still maintains its 45-degree angle with the 45-degree meridian of longitude, there has been no false torsion according to the spherical coordinate system.

was proved correct by the diplopia test. The patient, a diabetic, had recently acquired the paresis and did not suppress the false image.

If the normal eye is rotated upward and outward, upward and inward, and downward and inward, there is no objective appearance of torsion when the correct method of observation is used. When the normal eye is rotated far downward and outward, however, there is normally slight real intorsion. This may be due to action of the superior oblique, for it was absent in a patient with paresis of the superior oblique, although present in the opposite normal eye. In a patient with 4 arc degrees of left hypertropia in eyes down and left, due to weakness of the left inferior rectus, the normal intorsion in this quadrant was exaggerated when compared with the other side. Apparently, this exaggerated intorsion resulted from the efforts of the superior oblique in assisting the weak inferior rectus to turn the eye down.

Fig. 9.—*A*, spherical coordinate, viewed from the side.

B, spherical coordinate viewed "on edge." It then appears as a straight line. If the observer will sight along the direction of rotation of the eye, he will be sighting along the meridian of longitude over which the cornea is traveling. An imaginary line from the center of the cornea to a conjunctival vessel lying exactly in the direction of rotation of the eye will coincide with the meridian of longitude along which the cornea is moving. False torsion will not appear. Real torsion will show itself as a change of angle between the line from conjunctival vessel to center of cornea, and the direction of motion of the cornea, the spherical coordinate.



COMMENT

Most of the torsion seen objectively is caused by action of the synergist of the paretic muscle. The plane of muscle action identified by corneal torsion is the plane of action of the synergist.

The detection of torsion should be used as an adjunct to the cover test. If the cover test reveals, for example, an equal amount of right hypertropia in eyes up and left and in eyes down and left, it is difficult to determine whether the left superior rectus or the right superior oblique is paralyzed. Extorsion of the vertical corneal meridian will result from paresis of either of these muscles, but for paresis of the superior rectus the extorsion will appear in the upper fields, while for the paretic superior oblique it will appear in the lower fields.

To these two tests should be added the observation of head tilt and use of Bielschowsky's [8] head tilting test, as elucidated by Adler.[9] In this test, when the head is suddenly forcefully tilted to the paralyzed side, if the superior oblique is paretic, the paralyzed eye will shoot upward, owing to the unopposed efforts of the superior rectus to produce the normal postural intorsion for this position of the head.

SUMMARY

1. In order to see real torsion objectively, it is necessary to eliminate false torsion from the observation by using a spherical system of coordinates.

2. To employ a spherical system of coordinates, the eye must be rotated precisely along an imaginary line from a conjunctival vessel to the center of the pupil. The observer must sight along this line, keeping his eye directly over it and in line, as well, with the center of the eye.

CONCLUSIONS

The objective detection of torsion should take its place as an adjunct to the cover test and the observation of head tilt in the diagnosis of vertical strabismus.

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XEROPHTHALMIA

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THREE cases of xerophthalmia, an almost forgotten ocular disease in the United States, have been observed at the University of California Hospital eye clinic in the last five years. Two of the three resulted from antiallergenic diets; the third followed a congenital bile duct obstruction. In each case recognition of the characteristic eye lesions led to early diagnosis and to the successful treatment of the avitaminosis. In addition, two adult cases of vitamin A deficiency resulting from low vitamin intake in chronic alcoholism and one case in a 15-year-old boy with malnutrition were recognized from the presence of Bitot's spots.

Some of the terms used in connection with this disease have been variously interpreted; to avoid confusion, they will be defined according to their use in the ensuing discussion, as follows:

Xerophthalmia is the general term applied to a pure vitamin A deficiency disease of the eye characterized in its early stages by night blindness and a lack of conjunctival and corneal luster; a secondary conjunctivitis supervenes and accompanies increased conjunctival drying and such corneal changes as opacification, ulceration, and necrosis.

Xerosis is the term used to indicate drying of the conjunctival and corneal tissues from any cause. Xerosis in vitamin A deficiency has a singular appearance, as will be noted later in this paper.

Keratomalacia occurs in advanced xerophthalmia and refers to the softening, ulceration, and opacification of the cornea which develop as a result of prolonged vitamin A deficiency; it may terminate in perforation.

HISTORICAL REVIEW

Xerophthalmia has been a recognized clinical entity since the 19th century B. C., but the first accurate description of it was made by Albrecht von Graefe in 1866.[1] A sound experimental approach to the disease was made in 1906, when Falta and Noeggerath [2] reported the occurrence of conjunctivitis in rats on deficient diets. In 1908 Knapp [3] studied a series of poorly fed animals with bilateral ophthalmia characterized by corneal turbidity and ulceration. He predicted that the cause would be found to be dietary.

In 1912 Funk [4] suggested the name *vitamine* for certain essential nutritional elements, and in 1915 McCollum and Davis [5] produced ophthalmia and inanition

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in rats by giving them a fat-free diet and restored them to health by means of standard rat menus. McCollum * later contributed the term "xerophthalmia" and showed that the disease was due to lack of fat-soluble vitamin A. In 1920 Osborne and Mendel [8] reported their confirmatory experiences with 1,000 rats on vitamin-deficient diets. They found that the characteristic ophthalmia occurred exclusively in rats on diets deficient in vitamin A and that the eyes could be cured within a week by administration of only 100 mg. of butter fat. They noted that young deficient rats needed more vitamin A for treatment than mature deficient rats, and that when vitamin A was removed simultaneously from the diets of both young and mature rats, the disease symptoms appeared first in the young animals. A similar observation was later made on human subjects by Blegvad,[1] who reviewed the subject of xerophthalmia in 1924 and presented 447 cases he had collected in Denmark between 1909 and 1920. Infants from 3 to 8 months of age were found to be most susceptible; those younger than 3 months rarely developed the disease.

Distribution and Incidence.—Xerophthalmia is a result of subsistence on food low in vitamin A. Blessig (1866), cited by Leber,[9] saw many cases associated with Lenten fasting in Russia. Mori,[10] and later Ishihara,[11] found numerous cases in Japan, most of them in babies about a year old who were being weaned. In 1857 the members of Livingstone's [12] exploration party in South Africa suffered from the disorder, and McKenzie [13] observed a great many cases among South African natives. Pillat [14] studied 3,000 Chinese soldiers in 1929 and found 91 with xerophthalmia in one stage or another. Wright [15] reported keratomalacia as the commonest cause of preventable childhood blindness in India.

The most recent study of blindness in India was made by Somerset and Ghose [16] in 1950. They found xerophthalmia to be the etiologic agent in 8% of 1,431 cases of bilateral blindness, as compared with 5.2% of cases of blindness from trachoma. Lack of milk was believed to be the fundamental factor. Somerset † regarded the xerophthalmia chiefly as a manifestation of chronic deficiency disease and stated that no instances of pure avitaminosis were observed in the Bengal famine of 1943; emaciation developed swiftly, without the usual signs of deficiency in vitamin A, C, or D. Holmes [17] reported that he saw "several hundred" cases of keratomalacia during a visit to India in 1952. Field [18] described the immigrant Indians in Malaya as suffering from "xerophthalmia, night blindness, and multiple infections."

In 1930 Weech [19] recorded 13 cases of xerophthalmia in American children, and Spence [20] reported 17 cases in 1931. A search of the literature has revealed only one American report [27] since then, and it may certainly be assumed that the disease is now rare in this country.

CLINICAL CHARACTERISTICS

In 1929 Pillat [21] wrote an excellent essay on the clinical appearance of xerophthalmia in Chinese adults, and much of the following description has been excerpted from his paper.

Xerophthalmia develops characteristically in four stages, as follows:

1. Night blindness is the earliest symptom. It varies greatly in severity and may exist with or without xerosis.

* References 6 and 7.

† Somerset, E. J.: Personal communication to the author, from Calcutta.

2. Xerosis of the conjunctiva follows night blindness in most cases. The xerosis of vitamin A deficiency has four distinct components:

(*a*) Bitot's spot, described by Pillat,[22] is a triangular, white, foamy spot in the palpebral fissure, standing out from the otherwise normal bulbar conjunctiva, its base at the limbus and its apex directed toward the outer canthus. It usually appears temporally first, as a spot 3 to 4 mm. in diameter, and extends superiorly and nasally as the disease progresses.

(*b*) Plaque formation is the second component of conjunctival xerosis in vitamin A deficiency. The large, white, irregular plaque, which may be regarded as a giant Bitot spot, enlarges first toward the inferior fornix and then superiorly.

(*c*) Loss of luster is an early sign of conjunctival xerosis. In its subtler form the dryness can be accentuated by holding the lids open momentarily.

(*d*) Wrinkling in characteristic furrows concentric with the limbus is an invariable late manifestation of conjunctival xerosis in vitamin A deficiency and indicates a loss of conjunctival elasticity.

3. Xerosis of the corneal epithelium is the third stage in the development of xerophthalmia. It is divided into prexerosis and true, white xerosis. Prexerosis is characterized by loss of corneal luster and reduction in corneal sensitivity. True xerosis is an extension to the cornea of the conjunctival xerosis. Prexerosis is easily reversible but if untreated will progress to true xerosis.

4. Keratomalacia is the late, severe stage of xerophthalmia, in which the cornea becomes cloudy, soft, and ulcerative; perforation with subsequent panophthalmitis is a serious threat.

PATHOLOGY

Microscopic study of the scrapings from a Bitot spot shows large, keratotic epithelial cells with pale, indistinct cytoplasms and fragmented nuclei. Keratinized squamous epithelium has replaced the normal columnar conjunctival epithelium. Xerosis bacilli are numerous. According to Mori,[23] the conjunctival goblet cells are destroyed in the course of the xerotic process. Similar epidermoid changes in the epithelium of the lacrimal gland lead to a diminution of tears, and this contributes to the generally dry state of the conjunctival sac and encourages secondary infection. The ducts of the Meibomian glands show cystic dilatation and are filled with a fatty, glandular secretion and degenerated epithelial cells.

Wason[24] described the microscopic corneal changes as hyalinization of the epithelium, degeneration of Bowman's membrane, and infiltration of cells and edema fluid into the stroma. This is associated with invasion of blood vessels and fibroblastic proliferation. The epidermoid changes[25] are followed by trophic disturbances, corneal ulceration, and, ultimately, perforation unless the process is reversed. Secondary infection hastens the destructive process.

TREATMENT

In Peiping, Chu and Lin[26] treated nine patients (three infants and six adolescents) who displayed one degree or another of xerophthalmia. Improvement was always evident within two days of the initiation of parenteral treatment with vitamin A concentrate. The authors found that beneficial results from a single dose sometimes lasted as long as two months. When there was secondary infection, vitamin A alone would not stop the destructive process in the cornea. Spence[20] cured

xerophthalmia in its early stages by adding 10 cc. of cod liver oil to the diet daily. Somerset,‡ a recent investigator of this subject, wrote that once corneal ulceration had occurred, visually important scarring was inevitable. He felt that the mild diarrhea usually accompanying the disease made oral vitamin A therapy useless and that consequently the route of administration should be parenteral. He recommended a daily dose of not less than 100,000 units and stated that in early cases clinical response to this dose would be demonstrable within 24 hours. Somerset also reported seeing a considerable number of Bitot spots in Calcutta in children who showed no signs of avitaminosis. These lesions failed to respond to any type of therapy, including massive doses of multiple vitamins, and, in the author's opinion, could be regarded as sequelae in eyes in which the mucous glands had been destroyed in the course of some previous disease process.

REPORT OF CASES

Xerophthalmia in Three Infants.—Case 1 (P. E. #U154452).—The parents brought their 4-month-old son to the University of California clinic because of his yellow color. They had first noticed a slightly yellowish tinge to his skin eight days after birth. They stated that he was lethargic and had clay-colored stools. At 6 weeks of age his eyes had become red and the corneas cloudy. These signs had gradually increased in intensity. No vitamin supplements had been added to the formula.

The family history was negative.

Examination revealed a deeply jaundiced white child who was drowsy, irritable, and listless.

Eyes.—Bitot's spots and conjunctival wrinkling, more marked temporally, were seen in both eyes. Both corneas were gray and lusterless. A deeply staining, 3-mm. central ulcer involved the right cornea, and a hypopyon filled the lower third of the anterior chamber. There was no true ulceration of the left cornea, but there were several areas of superficial staining. The left anterior chamber was clear. Conjunctival redness made it difficult to tell whether or not the scleras were yellow.

Skin.—The skin was a deep yellow but clear.

Abdomen.—The liver was palpated 5 cm. below the rib cage.

Laboratory Studies.—Conjunctival smears showed numerous xerosis bacilli (Bacillus xerosis [Corynebacterium xerose]) and keratinized epithelial cells. The icterus index was 110.

Diagnosis.—Congenital biliary atresia; xerophthalmia with bilateral keratomalacia and corneal ulcer, right eye.

Treatment.—(1) Calciferol (Drisdol,§ containing vitamin A), 6 drops (0.2 cc.) orally daily for six days only; (2) multiple vitamin concentrate (vitamins A, B, D, E, and C), 0.5 cc. orally twice daily from sixth day until discharge from hospital; (3) sulfacetamide drops and ophthalmic vitamin A and D ointment (White's) in each eye four times a day; (4) atropine, 0.5%, 2 drops in each eye twice daily.

Clinical Course.—After one week of treatment the conjunctival redness had disappeared and the scleras were unmistakably yellow. At this time the vitamin A blood level was 30 I. U.‖ The left cornea was clear; the hypopyon had diminished in the right eye, and both conjunctivas

‡ Somerset, E. J.: Personal communication, from Calcutta.

§ Drisdol is a vitamin supplement which is distributed in two forms under one name: (1) Drisdol in propylene glycol, which is crystalline vitamin D_3 (calciferol) and contains 10,000 U. S. P. vitamin D units per gram, and (2) Drisdol with vitamin A in oil (water-dispersible), which contains 1,250 U. S. P. vitamin A units and 250 U. S. P. vitamin D units per drop. It might be helpful if these two preparations carried differentiating numbers after the name Drisdol or if they carried different names.

‖ Normal level, 50 to 150 I. U. per 100 cc. of plasma.

and corneas had more luster. Surgery was delayed until 14 days after admission because of an associated pneumonitis. A choledochoduodenostomy was then performed, and the patient was discharged five weeks after admission. The vitamin A blood level had returned to normal (79 I. U.). On a return visit, six months later, there was no jaundice and the eyes were normal except for a small central opacity in the right cornea. Reexamination five years later revealed little change in the corneal opacity.

CASE 2 (M. D. #U175410).—This 5-month-old baby was referred to the University of California Hospital by the family physician for the care of a persistent ulcer in the left eye.

History.—When the baby was 4 months old, the parents had first noticed an "irritation of his left eye." In the next few days both eyes had become swollen and red and the "surface looked rough." Their personal physician stained the left eye with fluorescein and found the cornea completely denuded of epithelium and deeply ulcerated slightly above the central pupillary area. Penicillin and sulfacetamide drops were administered. The cornea cleared around the ulcer in three or four days, but during the following week bronchopneumonia developed, with fever and a severe cough, and the baby was hospitalized for 16 days. While he was in the hospital, the ulcer was cauterized with iodine. The results were poor, and the cornea again became hazy over its entirety and failed to respond to instillation of atropine drops, oral use of chlortetracycline (Aureomycin), or foreign protein therapy with Omnadin.¶

The baby had presented a feeding problem since birth. He was given evaporated milk for the first weeks of life, and then goat's milk when he was found to be allergic to the canned milk. He was later shifted to Mull-Soy # because of wheezing, sneezing, and rhinitis. These symptoms disappeared, but there was no gain in weight. Supplementary feeding had consisted of the following: (1) ascorbic acid, one tablet daily; (2) an iron preparation, 5 drops (0.3 cc.) daily; (3) Drisdol (without vitamin A), 5 drops daily; (4) crushed pears and ½ oz. (15 gm.) barley daily, and (5) puréed carrots occasionally.

The maternal grandfather had asthma and hay fever.

Examination (on admission to University of California Hospital).—The infant was pale, slightly underdeveloped, but well nourished.

Eyes: The right eye had a Bitot spot on the temporal bulbar conjunctiva. The conjunctival sheen was decreased, and there were a few white, foamy flecks in the lower cul-de-sac but no wrinkling or furrowing.

The left eye had a 7-mm. central indolent ulcer, which stained deeply. The bulbar conjunctiva was dry and wrinkled, with many furrows concentric with the limbus; the desiccation was more prominent temporally, where there was a large Bitot spot.

Skin: The skin was sallow and pale, and there was a fine, discrete rash over the face and neck.

Abdomen: The liver was palpable 4 cm. below the rib cage.

Laboratory Studies: Scrapings from the conjunctiva showed keratinized conjunctival epithelium and many xerosis bacilli. The vitamin A blood level was 15 I. U. per 100 cc.

Diagnosis.—Avitaminosis A, with (*a*) xerophthalmia with corneal ulcer, left eye, and (*b*) dermatitis.

Treatment.—(1) Vitamin A, 100,000 units intramuscularly, single injection; (2) ophthalmic vitamin A and D ointment (White's), three times daily in each eye; (3) vitamins A and D (Zymadrops), 25 drops (0.9 cc.) orally daily for nine days, and 15 drops daily thereafter.

Clinical Course.—There was a spectacular improvement in the eyes within 48 hours, and the skin rash cleared in 5 days. In one week the Bitot spots had disappeared and the corneas and conjunctivas had regained their normal luster. In three weeks the vitamin A blood level was

¶ A sterile solution of protein substances obtained from nonpathogenic bacteria.

Mull-Soy is a liquid hypoallergenic soybean food manufactured by the Borden Company for use as a milk replacement in feeding infants, children, and adults. It closely approximates whole cow's milk in fat, protein, carbohydrate, and mineral content when diluted with an equal quantity of water. Since vitamins may be specifically allergenic, Mull-Soy contains none. In infant feeding the required amounts of iron and vitamins must be provided from other sources, as recommended by the physician.

100 I. U. per 100 cc. The corneal ulcer in the left eye cicatrized gradually. Follow-up clinical photographs taken three years later showed a normal right eye and a small corneal scar in the left eye.

Case 3. (R. B. #U187841).—This 5-month-old child was admitted to the University of California Hospital because of red eyes, allergic manifestations, a feeding problem, and a bulging fontanel. He had had red eyes since the age of one week, and there had been associated tearing, a scanty discharge, and some slight progression of the redness during the weeks prior to hospital admission. The eyes had been treated with penicillin drops, without benefit.

The baby had been considered a feeding problem from birth and had gained weight very slowly. Because of a suspected allergy to his formula, he was given Mull-Soy and Drisdol (without vitamin A) from the age of one week. When he was 4 months old, the mother noticed half-moon-shaped white areas temporally over the white of each eye. These seemed to increase in size during the ensuing weeks. Two days prior to admission the referring physician noted a bulging anterior fontanel. On this basis the child was admitted to the neurological service.

Examination revealed a small, active, pale, 5-month-old infant who seemed neither acutely nor chronically ill.

Head.—The head measured 39.7 cm. (third percentile below normal) in its greatest diameter. The anterior fontanel measured 4 by 6 cm. and was bulging; the posterior fontanel was closed.

Eyes.—The corneas showed a lack of luster but no staining and no ulceration. There were typical Bitot spots temporally in both eyes. The conjunctivas in these areas were dry and wrinkled, with furrows concentric to the limbus and extending around the superior limbus to the nasal side. There were a few floating, white, dry flecks in the lower cul-de-sac of each eye.

Skin.—The skin was smooth and clear, and there were no other clinical signs of vitamin A deficiency.

X-Rays.—Skull films showed widening of the cranial sutures typical of increased intracranial pressure.

Laboratory Studies.—The conjunctival scrapings showed many xerosis bacilli and keratinized epithelial cells; blood agar cultures from the conjunctivas were negative.

Diagnosis.—Xerophthalmia.

Treatment.—(1) ascorbic acid, 10% solution, 10 drops (0.6 cc.) orally twice daily; (2) A and D vitamin concentrate (haliver oil, unfortified), 20 drops (1.3 cc.) orally daily.

Clinical Course.—The patient was discharged from the hospital one day after specific treatment was instituted and was not seen again by the University of California Hospital staff. Treatment was to be continued at home, however, and the referring physician reported by letter that the child's eyes cleared up within 10 days. They have remained clear to date, and the child has been in good physical condition.

Avitaminosis A in Two Adults and One Adolescent Boy.—Case 4 (private patient).—A 43-year-old housewife had been a chronic alcoholic for several years. Her eye complaints included poor vision, night blindness, and ocular inflammation, and irritation. Examination revealed a corrected visual acuity of 20/30+ in both eyes. Slit-lamp examination revealed well-developed Bitot spots temporally in both eyes and the generalized diminution of conjunctival and corneal luster characteristic of prexerosis. Scrapings from the spots showed keratinization of the epithelium and abundant xerosis bacilli.

The patient's general nutrition seemed fair, but her personal physician concurred in the diagnosis of avitaminosis A and placed her on vitamin A supplements and therapeutic Multi-Vitamin capsules. He was unable to modify her chronic alcoholism in any way, but over a 3-month treatment period there was improvement in the ocular signs. They did not entirely disappear, but vision rose to 20/25+ in each eye, probably as a result of improved corneal transparency. The patient did not notice any change in her poor night vision.

Case 5 (private patient).—A 52-year-old laborer and chronic alcoholic of many years' duration was hospitalized because of the clinical signs of pellagra. He was referred for ophthalmological study because of poor vision. A bilateral neuritis with characteristic central scotomas was found and was believed to be a result of vitamin B_1 deficiency. The external eye signs of prexerosis were also in evidence, including Bitot spots and loss of corneal luster. Epi-

thelial scrapings from the spots showed advanced keratinization of the epithelial cells and overgrowth of xerosis bacilli. Treatment with vitamin supplements over a period of several months led first to disappearance of the prexerotic signs and eventually to partial recovery of central vision.

CASE 6 (private patient).—A 15-year-old farm boy was hospitalized because of advanced malnutrition. Analysis of his diet indicated a dietary insufficiency extending over a period of more than six months, the result of extreme poverty coincident with his father's illness and consequent crop failure. The child showed no fundus or field changes but had well-developed Bitot spots, with mild but definite corneal epithelial changes. On an adequate diet supplemented with 25,000 units of vitamin A daily, the eye changes gradually disappeared over a six-week period.

COMMENT

The first case in this series was an example of the development of xerophthalmia consequent to an inadequate intake of vitamin A and to its lack of absorption in the gastrointestinal tract. Congenital atresia of the common bile duct led to failure of the bile to enter the duodenum. In the absence of bile there was no absorption of the vitamin A present in the formula.

The second case arose from a dietary deficiency in a well-organized household. Mull-Soy was used effectively to control the allergic symptoms, but the supplementary vitamins did not include vitamin A. The large corneal ulcer in the left eye healed with only a relatively small residual leucoma; the keratomalacia in this case was thus at least partially reversible. As in Case 1, the complicating pneumonia was a logical consequence of the inevitable keratinization of the bronchial epithelium. At the time of writing this patient has a small, central opacity of the anterior capsule of the lens. A similar sequela from severe cases was recorded by Pillat.[22]

The third care demonstrated that xerophthalmia can masquerade as a catarrhal conjunctivitis, a feeding problem, or a central nervous system disease. Once again, Mull-Soy was used as the nonallergenic formula with vitamin supplementation in the form of Drisdol of the type containing vitamin D only.

The enlarged liver in Cases 1 and 2 and the widening of the cranial sutures in Case 3 were interesting associated manifestations. Cornfield and Cooke[27] observed both these signs in their case. Pertinent to the small head size and the bulging fontanel, it is noteworthy that Wolbach and Hegsted[28] restricted vitamin A in the chick and observed balanced retardation of osseous growth and failure of the cranial bones to keep pace with brain growth; this led to herniation of the cerebellum and cerebrum, with the same signs as those shown by a space-occupying lesion of the brain.

In substantiation of the theory that a child cannot be sustained in good health for any appreciable period without its essential nutritional elements, all three infants in this small series developed eye abnormalities before they were 3 months old. None of them showed any hair-follicle hyperkeratosis, but the adult with pellagrous signs had typical hyperkeratotic skin changes. This observation is interesting in the light of the work on adults done by Frazier and Hu[29]; the skins of their patients were dry and rough several weeks before the ocular symptoms appeared. In contrast to the Asiatic disease, as described by Pillat,[30] in which 75% of the patients with keratomalacia showed conjunctival pigmentation in the lower fornix, this sign was entirely absent from the group reported here.

In view of the importance of an early ophthalmologic diagnosis of xerophthalmia, differentiation between a Bitot spot and a neoplastic epithelial plaque is important. During the course of this study, a 54-year-old woman was seen with bilateral keratinized epithelial plaques located at the temporal limbus and simulating grossly Bitot's spots. Scrapings from the lesions contained cornified epithelial cells without xerosis bacilli. The cornea and conjunctiva showed no lack of luster. This is regarded as the most important differential sign between the two conditions. There was no response to large doses of vitamin A over prolonged periods. For cosmetic reasons, the plaques were removed surgically, and microscopic examination verified the clinical diagnosis of neoplastic epithelial plaque. Other instances of conjunctival and corneal keratinization were observed during the period of this study in connection with such cicatrizing diseases as ocular pemphigus, trachoma, and membranous conjunctivitis; none of these presented any problems in differential diagnosis.

Hickey [31] reported a hyperkeratinization of the Meibomian glands in patients with decreased vitamin A utilization which he believed led to chalazion formation. In the treatment of early chalazia and for the prevention of recurrence following chalazion excision, he found the daily administration of 50,000 to 100,000 units of vitamin A a successful procedure. Some support for Hickey's theory may accrue from the apparent frequency with which chalazia occurred in the malnourished, vitamin-deficient European children brought to this country in the immediate postwar period. Three such children suffering from multiple chalazia were seen by me and my associates in our offices. On the assumption that hyperkeratinization of the hair follicles may induce acne, Straumfjord [32] treated a series of cases of this condition with vitamin A; according to his report, most of them improved.

Xerophthalmia and other severe avitaminoses are rare in the United States today, but subclinical vitamin deficiencies are believed to be relatively common [33] and to cause considerable chronic mental and physical ill-health. Contributing to these subclinical states are chronic illnesses in which there is anorexia and decreased physiological effectiveness with respect to the absorption, storage, and utilization of vitamins. Foremost in this group of illnesses are alcoholism, dysentery, hepatitis, and fibrocystic disease of the pancreas. Special attention should be given to diet in all these conditions. The current wave of dieting for weight reduction in the United States also calls for watchfulness for nutritional disease. The inhibitory effect of liquid petrolatum U. S. P. on vitamin A absorption should also be borne in mind. Steigmann and associates [34] found that more than 2.5 cc. of liquid petrolatum taken three times during the day decreased vitamin A absorption in the gastrointestinal tract; they determined also that the usual bedtime dose of 30 cc. had no effect on diurnal vitamin A blood levels.

Although children with borderline malnutrition are still to be seen in this country, the diagnosis of xerophthalmia is extremely uncommon. The reason for this is not clear, but it may be that almost total vitamin A exclusion is necessary to produce the eye signs. At the present time I am observing a 19-month-old child who has had no food containing vitamin A for 12 months; the eyes and skin are still normal but the vitamin A blood level is 49 I. U. It is possible also that some mild cases are overlooked because of unfamiliarity on the part of many physicians with the clinical signs of the disease.

A note of caution should be sounded as to the danger of hypervitaminosis A due to overdosage. Caffey [36] reported seven cases of vitamin A poisoning in infants and young children; all of them displayed hyperirritability, tender swellings, and hyperostoses, especially of the ulnas and metatarsals. Since then, reports of 14 additional cases have appeared in the literature.[37] The vitamin A requirement for man has not yet been determined,* but the daily intake recommended by the Food and Drug Nutrition Board [38] is 1,500 I. U. per day for infants and 5,000 I. U. per day for adults.

SUMMARY AND CONCLUSIONS

Three cases of xerophthalmia in infants are reported, one due to congenital bile duct atresia, the other two to antiallergenic diets without proper vitamin A supplementation. In addition, three cases of prexerosis in adults are described, two of them in association with chronic alcoholism and the third, that of an adolescent boy, in association with the general malnutrition.

Xerophthalmia is manifestly rare in the United States at the present time, but it is suggested that a number of cases may be overlooked because of lack of familiarity on the part of ophthalmologists and pediatricians with the early ocular signs. These signs are discussed in detail.

Ophthalmologists should be alert for evidence of avitaminosis A in infants with special feeding problems, in children and adults on reducing or antiallergenic diets, and in chronic alcoholics and patients with gastrointestinal and liver diseases.

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FUNDUS LESIONS WITH DISSEMINATED LUPUS ERYTHEMATOSUS

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DISSEMINATED lupus erythematosus is a febrile, usually fatal, disease involving the ground substance of connective tissue. It may attack any organ of the body, and thereby gives rise to an extremely polymorphic group of symptoms.

Because of this generalized predilection for connective tissue, Klemperer, Pollack, and Baehr have classified disseminated lupus erythematosus as a "collagen disease," along with rheumatic fever, rheumatoid arthritis, periarteritis nodosa, generalized scleroderma, and dermatomyositis. Klemperer has emphasized that this classification is purely a morphologic one; it has no pathogenetic significance and does not imply that these conditions have a common etiology.

Disseminated lupus erythematosus must be distinguished from tuberculous lupus and discoid lupus (lupus erythematosus discoides), which are purely dermatologic conditions.

Reference to ocular lesions with lupus erythematosus is infrequent, and the cases which have been confirmed by histologic examination are very rare.

The case of lupus erythematosus to be reported here is that of a young woman whose fundus lesions we have been able to observe for a year. The protracted course, interrupted by remissions, the frequency of the ocular examinations, and the availability of histologic material provided an unusual opportunity to make an exact study of the ocular lesions in the course of the disease.

REPORT OF A CASE

First Admission.—The patient was a woman of 26 without previously significant disease.

Eight months, and again one and a half months, before her hospitalization there had been febrile episodes accompanied by grip, with asthenia, anorexia, swelling of the joints, and, with the second episode, an erythematous dermatosis. These two episodes remitted spontaneously.

On Jan. 24, 1951, the patient entered the hospital (medical service, Prof. P. Govaerts) presenting a recurrence of fever, with temperatures reaching 40 C. (104 F.), accompanied by the same symptoms—asthenia; anorexia; erythematosquamous lesions of the face, lids, ears, forearms, and legs, with painful joints; signs of endocarditis, and pulmonary congestion. A biopsy of the skin, performed by Dr. van der Meiren, confirmed the diagnosis of disseminated lupus erythematosus. (An "upholstery-tacks" formation was observed at the level of the epidermis, with erosion of the basal layers; however, no "hematoxylin bodies" could be found.)

Translated from the French by David G. Cogan, M.D., Boston.

From the Department of Pathology (Prof. P. Gerard), the Ophthalmic Clinic (Prof. L. Coppez), and the Medical Clinic (Prof. P. Govaerts), of the University of Brussels.

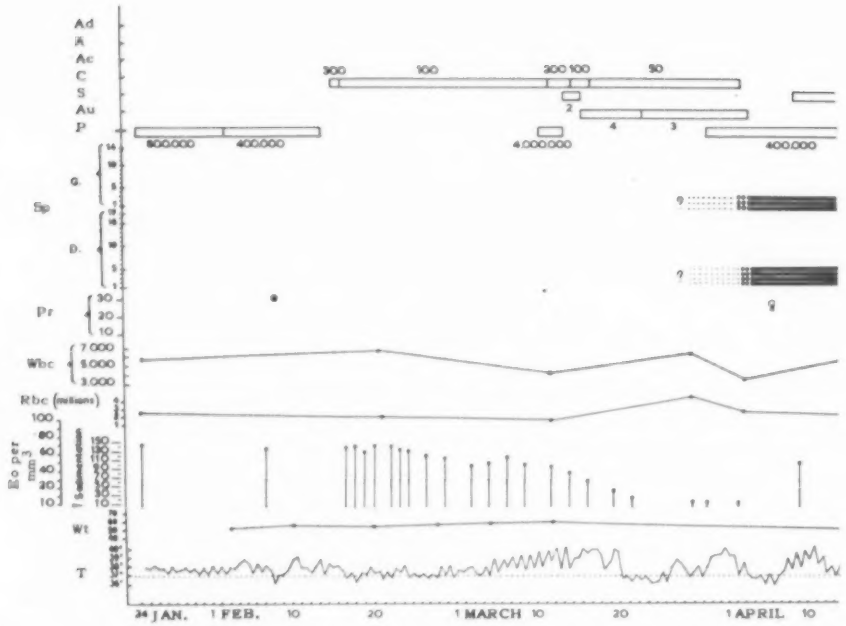


Fig. 1.—Course of temperature, weight, sedimentation rate, number of red and white blood cells, and fundus

In this Figure and in Figure 3, the following abbreviations are used: *Ad*, total adrenal extract; *A*, acetylsalicylic tomycin, grams a day; *Au*, oxytetracycline (Aureomycin), grams a day; *P*, penicillin, units daily; *Sp*, white spots in globulin); *Wbc*, white blood cells; *Rbc*, red blood cells; *Eo*, eosinophiles (broken line with crosses), eosinophiles ture, degrees (C.).

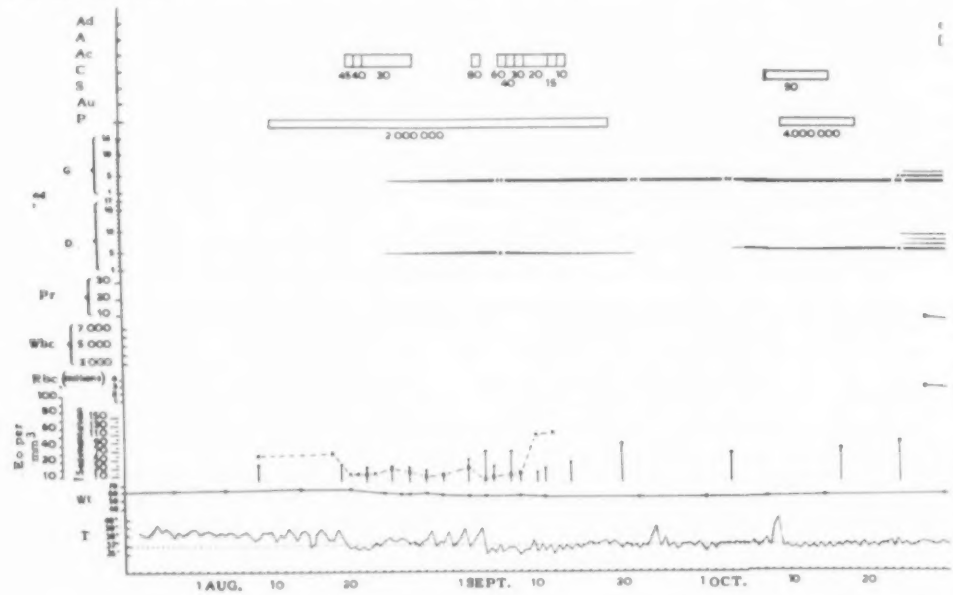
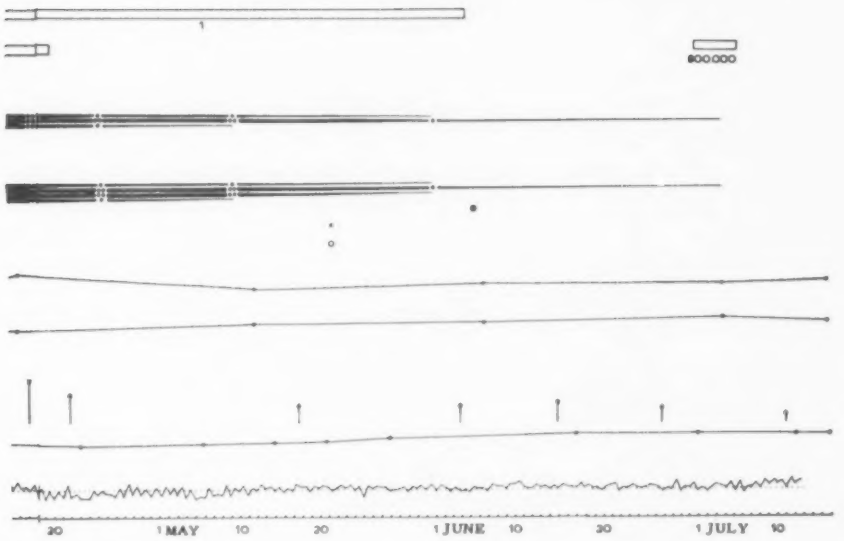
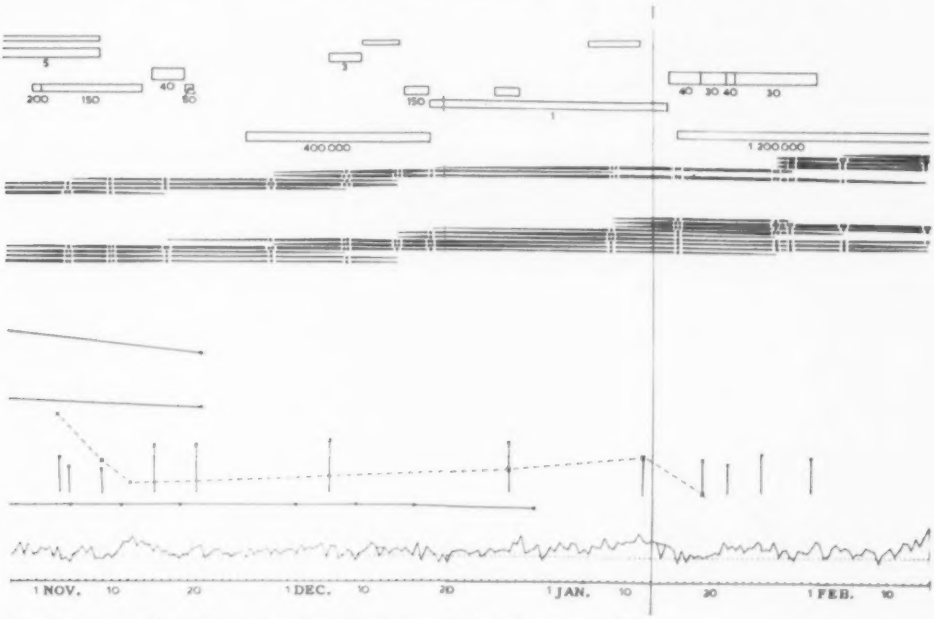


Fig. 3.—Course of temperature, weight, sedimentation rate, number of



lesions during first visit.

acid (Aspirin), grains a day; *Ac*, corticotropin (ACTH), milligrams a day; *C*, cortisone, milligrams a day; *S*, strep-fundus; *G*, left eye; *D*, right eye; *Pr*, blood protein, grams per 1,000 cc. (line of crosses, albumin; line of circles, per cubic millimeter; *sed*, sedimentation rate (arrows), millimeters in one hour; *wt*, weight, kilograms; *T*, tempera-



eosinophiles per cubic millimeter, and fundus lesions during the second visit.

The patient was treated with cortisone (6 gm. from Feb. 16 to April 2, 1951), with the addition of various antibiotics (penicillin, chlortetracycline [Aureomycin], and streptomycin) because of the occurrence of a staphylococcic septicemia. The patient was discharged very much improved and afebrile on July 20. The sedimentation rate had fallen to 35 mm. in one hour (145 mm. on admission). It is noteworthy that she had several epileptic crises during this admission, in March, 1951 (Fig. 1).

Ocular Examination: We saw the patient for the first time on April 17. The visual acuity was 10/10 in each eye. The anterior segments were normal. In the fundus, small white spots, round or polygonal, with sharp edges, and measuring one-sixth the diameter of the disc, were disseminated throughout both retinas. These spots showed no peripheral pigmentation. They were situated within a short distance of the large vessels but never covered them. There were four such spots in the right eye and three in the left eye (Fig. 2*A*). There were no hemorrhages;

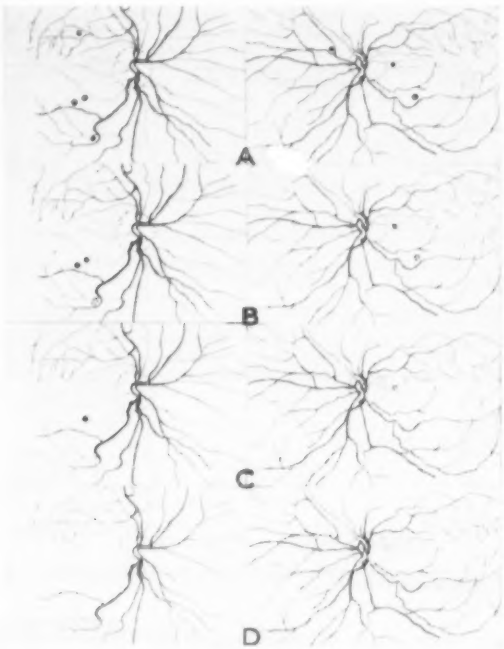


Fig. 2.—Ophthalmoscopic lesions. Diagrams made on April 17, May 16, June 2, and July 5, 1951.

the discs were not edematous; the vessels were normal. The pressure of the central retinal artery was 25/80 gm. (Bailliart units) in the right eye and 25/85 gm. in the left eye.

By April 25, the lesions had markedly regressed. On the right two white spots persisted; the other two were very pale, being hardly visible. On the left one spot persisted; the other two had regressed. At this time the patient had been afebrile for the past eight days and remained so until discharged. The weight curve rose (gain of 14 kg.); the pulmonary signs had disappeared. The joint pains and the cardiac murmur persisted.

Ophthalmoscopic examinations on May 16, June 2, and July 5 showed progressive disappearance of the fundus lesions.

May 16. Two lesions on the right were markedly regressive; on the left a lesion persisted but was also regressive (Fig. 2*B*).

June 2. On the right there was only one lesion and this indistinct; on the left there was one lesion, which was disappearing (Fig. 2*C*).

July 5. Both fundi were entirely normal (Fig. 2*D*).

Second Admission.—Four days after her discharge the patient had a recurrence of the fever. The anorexia and cutaneous eruption reappeared. The patient was readmitted to the hospital. Penicillin and streptomycin were without effect. Treatment with corticotropin was begun on Aug. 18, followed by a course of cortisone and a second series of injections of corticotropin (up to Feb. 1, 1952). Fifteen days after beginning of the treatment the general condition was markedly improved, with a fall in temperature, lessening of the anorexia and asthenia, disappearance of joint pains, regression of the cutaneous lesions, and increase in weight up to Sept. 26, 1951 (Fig. 3). From Oct. 28 the general condition became progressively worse, showing no remission despite all therapeutic measures. On Jan. 28, 1952, the general state of the patient

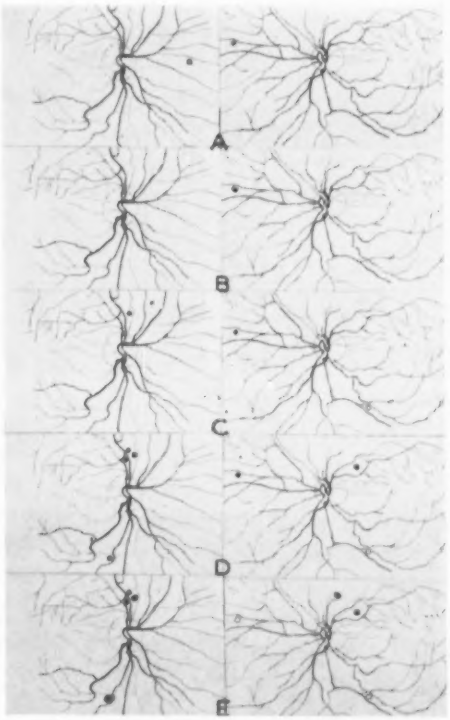


Fig. 4.—Ophthalmoscopic lesions. Diagrams made on Sept. 6, Sept. 22, Oct. 23, Nov. 5, and Nov. 11, 1951.

was very poor. Her complexion was pale; she was asthenic and anorexic. She presented an edematous infiltration of the skin and a pleural effusion. The lupus lesions of the skin were striking, and the temperature rose. By Feb. 2 the general state had further worsened, and the patient died on Feb. 15, 1952.

Ocular Examination: A month after the second admission (Aug. 23) the fundi were entirely normal. On Sept. 6 a retinal lesion similar to that noted in the previous examination had appeared in each eye (Fig. 4*A*). The subsequent examinations (Sept. 22 and Oct. 13) revealed rapid disappearance of the spots in the right eye, without the appearance of any new lesions (Fig. 4*B*). In the left eye the spots continued up to Nov. 17, 1951. At this time after the course of corticotropin, the patient showed considerable improvement in both general and local signs,

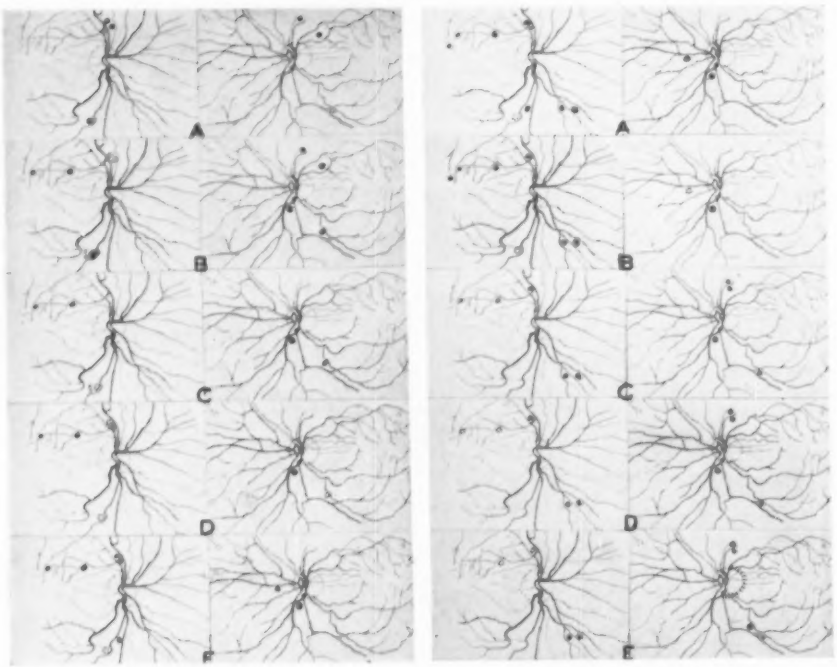


Fig. 5.—Ophthalmoscopic lesions. Diagrams made on Nov. 17, Dec. 8, Dec. 14, and Dec. 18, 1951, and Jan. 8, 1952.

Fig. 6.—Ophthalmoscopic lesions. Diagrams made on Jan. 16, Jan. 26, Jan. 30, Feb. 5, and Feb. 15, 1952.

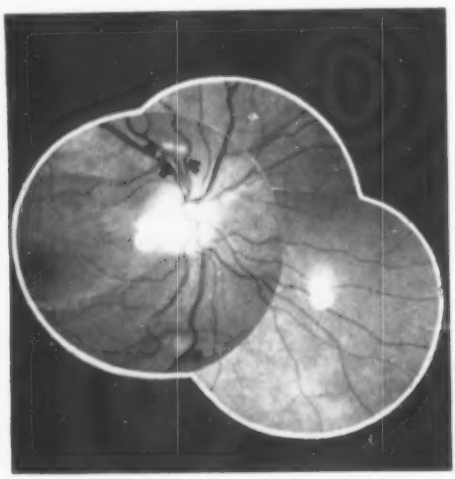


Fig. 7.—Photograph of the right fundus on Nov. 7, 1951. Note four white spots.

and this improvement lasted from Sept. 10 to Oct. 28. On Oct. 23, after the dermatologic lesions and the asthenia had recurred, the fundus showed two new typical spots (Fig. 4*C*). By Nov. 5 the number of spots in the eye had again increased, four on the right and three on the left (Fig. 4*D*), and remained, the number varying from 7 to 10 up to the time of the patient's death. Figures 4, 5, and 6 show the topography and the evolution of the lesions of the fundus during the second admission (see also Figure 3).

This aggravation of the ocular status accompanied an aggravation of the general state: From Oct. 28 on the temperature rose again, the articular pain reappeared, and the cutaneous lesions increased. In Figures 1 and 3 we have indicated, by way of comparison, the course of the temperature, the weight, the sedimentation rate, and the ocular lesions. We have similarly indicated the principal therapeutic procedures.*

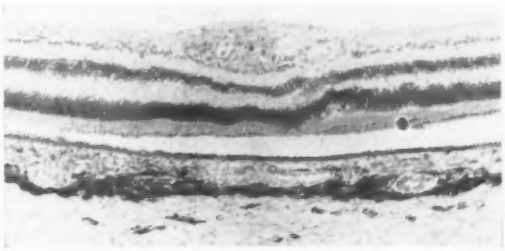


Fig. 8.—Histologic appearance of the numerous "cytoid" bodies, involving considerable hypertrophy of the nerve fiber layer of the retina. The ganglion cells are diminished corresponding to the mass of cytoid bodies.

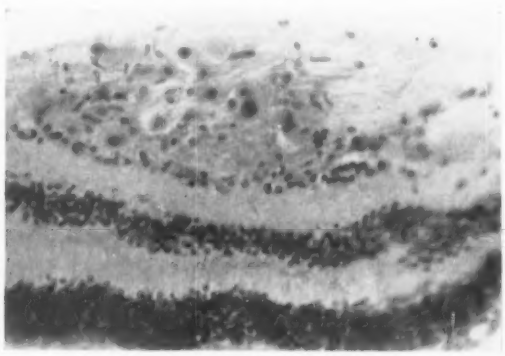


Fig. 9.—Same lesions as those shown in Figure 4, with high magnification. The cytoid bodies are visible, having an irregular form, certain ones of which contain in their center a more densely stained area.

In the course of our ocular examinations we never observed a white spot in the region of the macula. These lesions were always situated less than 4 disc diameters from the disc, very often along a vessel, sometimes between an artery and a vein. Only once did we see a white spot cover a small retinal vessel, but never did we find a spot beneath a vessel.

Although the total number of spots in the retina did not vary greatly in the last three months, it is of interest that each one underwent a typical evolution: Scarcely visible at first, it would increase perceptibly in distinctness and in pattern, then become pale, regress, and disappear. This

* The clinical and histologic details in this case have been noted elsewhere (Govaerts and associates).

disappearance was complete. There was a conspicuous absence of pigmentation. But if the evolutionary aspect of these spots was always similar, their duration was very variable. We have seen some of them appear and disappear in 35 days, while others had a cycle lasting as long as 81 days (Figs. 1 and 3). We saw a single retinal hemorrhage adjacent to a typical white spot in the right fundus (Jan. 16, 1952); this disappeared in less than 10 days. Papillary edema was noted on the first admission (April 3, 1951); 14 days later it had disappeared and never reappeared. At the last examination, a few hours before the death of the patient, we found blurring of the left papillary border and slight dilatation of the veins.

No other ocular lesion was noted clinically; we found no anomalies of the anterior segments; there was no involvement of the conjunctiva or of the uvea. The ocular motility was always normal.

Anatomicopathological Examination.—In the skin were found the "hematoxylin bodies" which are pathognomonic of disseminated lupus erythematosus (Gross, Klemperer). Besides, we observed the "wire-loop" lesions in the glomerular layers of the kidney, along with periarterial fibrosis in the spleen. Lesions of the last two types are very common in lupus erythematosus but may be encountered in other conditions.

The eyes were removed a few hours after death and fixed in Zenker's solution. One was embedded in paraffin and the other in celloidin. Serial sections were cut at 10 to 15 μ and

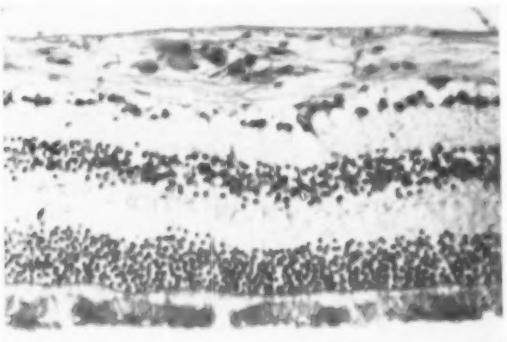


Fig. 10.—Mass of three "cytoid" bodies, not causing hypertrophy of the nerve fiber layer.

stained variously: with hemalum and eosin, Masson's trichrome stain, toluidine blue, and the MacManus and Feulgen methods.

The various layers of the retina presented a normal arrangement. Some regions showed zones of hypertrophy of the nerve fiber layers, producing an ovoid shape of the section. These zones were made up of the conglomerations of "cytoid bodies": globular elements situated between the nerve fibers, the volume of which at times was twice that of a ganglion cell. Certain of these bodies were made up of a mass of irregular form, taking acid stains (eosin) uniformly; others (Figs. 8 and 9) presented in addition a denser zone of staining in the center, which did not have the properties of a nucleus (Feulgen-negative; acidophilic).

These cytoid bodies, sometimes grouped in a tremendous conglomeration, corresponded to the white spots seen in the fundus. Some groups of two or three cytoid bodies did not raise the surface of the fiber layer and were probably not visible ophthalmoscopically (Fig. 10).

Neuroglial cells were found in these conglomerations in variable numbers—sometimes very abundant, sometimes scarcely increased in number. Corresponding to the conglomerations of the cytoid bodies the number of ganglion cells was decidedly diminished. These conglomerations were sometimes situated at the level of a vessel, but we have never seen any immediately connected with the branches of a vascular tree.

Certain retinal and choroidal vessels showed slight thickening of their walls accompanied by hyaline degeneration beneath the endothelium.

The other layers of the retina, the sclera, and the optic nerve were normal.

The choroid, by contrast, showed an infiltration with mononuclear cells, analogous to that described by Friedenwald and Rones in septic choroiditis—some lymphocytes with some large monocytes and some plasmacytes.

COMMENT

The fundus lesions which we have observed clinically in the course of disseminated lupus erythematosus have been described in the English literature under the name of "cotton-wool" exudates. They have also been noted in the German literature (Bergmeister, in 1929, was the first to note them) and occasionally in the French literature (Dollfus).

These soft white spots of the ocular fundi are found ophthmalmoscopically in other diseases: septic retinitis of Roth, leukemia, serum sickness, dermatomyositis, periarteritis nodosa, and hypertensive retinopathy.

Anatomic studies of the eyes of patients with lupus erythematosus have been reported six times. Typical cytoid bodies have been found four times: first by Kurz, in 1938; then by Maumenee, in 1940 (five cases), Cordes and Aiken, in 1947, and Aiello, in 1951. Goldstein and Wexler (1932) found only postneuritic and retinal atrophy. In the case of Semon and Wolff (1933) there were only inflammatory lesions of the choroid and subretinal exudate.

These cytoid bodies are not specific for lupus erythematosus. They have been found likewise in the retina in septic retinitis, periarteritis nodosa (Friedenwald and Rones), leukemic retinopathy, hypertensive retinopathy, and retinal tears (Parsons), and in the optic nerve or nerve head in papilledema, optic neuritis, and glioma of the chiasm or of the optic nerve (Verhoeff, P. Martin, and Cushing). These cytoid bodies have been interpreted as hypertrophic nerve fibers or as swollen and degenerated glial cells (Friedenwald).

Our observations are of note in that few eyes with lupus erythematosus have been studied histologically and, especially, in that we were able to follow regularly, for 10 months, the evolution of the ophthalmoscopic lesions. We have been able to establish definitely that these spots (conglomeration of cytoid bodies) have a cyclic evolution: appearance of a soft spot, sharpening of the ophthalmoscopic appearance, and period of stabilization, regression, and eventual disappearance, without a trace being left. The duration of the cycle and the size of the lesion are variable for different elements. These spots have a dimension varying from one-sixth to one-tenth the disc diameter. They maintain a quite constant diameter during their entire evolution. The only variable element is the intensity of the whitish color.

We have been unable to establish the factors conditioning the characteristic features of each lesion (size, duration of the cycle), but we can state that there is no parallelism between these two features. They do not appear to be influenced by the severity of the general state. None of the therapeutic measures tried (notably corticotropin and cortisone) had any effect on the evolution of the ocular lesions.

The periodic examinations enabled us to determine the variations in the total number of white spots in the fundus. These variations in the number of the lesions result from the progressive disappearance of some, following their cyclic evolution, and the continual appearance of new ones. At other times, on the contrary, some of the visible spots disappear without the occurrence of new exudates.

During the patient's first hospitalization (from April through July, 1951) the general state improved to the extent that the patient was able to leave the hospital. We noted at this time a progressive diminution in the number of elements and their complete disappearance. Nor did any of the same lesions reappear.

In the course of the second admission, the general state of the patient was at first improved, and during this brief period (from Sept. 10 to Oct. 28) there were no new lesions. Simultaneously, one of the two spots noted a few days after the readmission became veiled. From the time the general symptoms worsened to the death of the patient, i. e., from Oct. 28 to Feb. 15 (Fig. 5), we saw new lesions continually replacing those that had disappeared. We therefore conclude that a certain parallelism exists between the appearance of a conglomeration of cytoid bodies and the gravity of the general state.

In the literature there is explicit reference to the occurrence of "cotton-wool" exudates. Aiello identified the white spots which he saw appear in the eyes of his patient over a three-month period as being conglomerations of "cytoid bodies." In one of the four cases of lupus erythematosus reported by Keil, soft white spots appeared in the fundus shortly before death. Dollfus noted the increase in number of the whitish "exudates" in one patient with lupus erythematosus. Similar observations were made by Koch and McGuire.

Disappearance of the fundus lesions has been reported by other authors. In the discussion of Baehr and Pollack's communication, Longcope stated he had seen the small white spots of the fundus disappear in one patient with lupus erythematosus. Cluxton and Krause noted paling and attenuation of the lesions in the evolution of a case of lupus erythematosus. In a brief analysis of two cases of lupus erythematosus, Landowski reported the appearance and disappearance of the white spots in the fundus. (We did not check the case of Ambramowicz and Dulewicz, who noted variations in the number of fundus lesions. Theses authors considered these lesions to be like those of the guttate retinitis of Dimmer occurring with arteriosclerosis, and not like "cotton-wool" exudates corresponding to the conglomerations of "cytoid bodies").

In reviewing these various observations, we have noted that the appearance and increase of the number of spots have coincided with an aggravation of the general state (Aiello, Keil, Dollfus), while the disappearance or the attenuation of the ocular lesions accompanied a remission in the course of the disease (Cluxton and Krause, Longcope; personal observation, Figs. 1 and 3). These last authors also noted this coincidence.

Although not very explicit on the point, these several cases from the literature corroborate our impression of the parallelism between the appearance of the retinal spots and the aggravation of the general state.

SUMMARY AND CONCLUSIONS

Clinical observations of the eyes of a patient with lupus erythematosus over a period of one year, with an ultimate anatomic study, are summarized as follows:

1. Histologic examination has confirmed the previously rare observations on lupus erythematosus. The "cotton-wool" white spots, visible with the ophthalmoscope and described especially in the English literature, are due to conglomerations of "cytoid bodies" situated in the nerve fiber layer of the retina.

2. We have been able to establish a parallelism between the appearance of the retinal spots and the aggravation of the general state.

3. The prolonged course and the frequency of the ophthalmoscopic examinations have enabled us to recognize a typical cycle of the "cotton-wool" exudates. They disappeared, without leaving a trace, after a time varying from 35 to 81 days. This cycle does not appear to have any connection with the evolution of the general state.

It is concluded that the casual factor of the retinal lesion determines simply the appearance of the cytoid bodies, but not their evolution.

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ORBITAL AND TRANSORBITAL STAB WOUNDS

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IT IS NOT rare for orbital stab wounds to become fatal if no specific intervention is made. This is due to the common occurrence of additional, transorbital complications. Nevertheless, no particular attention has been paid to this type of lesion; in the ophthalmological and neurosurgical literature the contributions to the discussion of the subject are usually confined to case reports.

It is characteristic of these lesions that the external wound is small and that the track of the stabbing instrument is long and narrow, with an irregular course, due to transient displacement of the tissue at the moment of injury. The commoner complications are hemorrhage and infection. Stab wounds may readily result in an external closure of the wound and retention of secretion, so that favorable conditions may develop for the growth of anaerobic bacteria, such as Clostridium tetani.

Orbital stab wounds may be caused by pitchforks, pencils, twigs, etc., which may give rise to both direct and indirect injury of the orbital contents (the eyeball, vessels, nerves, muscles, and lacrimal gland) and, after penetration of the orbital wall, to injury of adjacent structures (the brain and its membranes, the internal carotid artery, and the venous sinuses). An orbital stab wound must be regarded as a serious and dangerous lesion, even though it may appear to be of a superficial nature and is not primarily associated with signs of intracranial complications. Accordingly, it should never be interpreted as an isolated lesion of the eye and the orbital contents.

Owing to the close proximity of the paranasal air sinuses, which are separated from the orbit only by the thin lamina papyracea, infection from the nose may occur if the lamina is damaged.

The various types of infection which may occur are collateral edema or phlegmon of the orbit, meningitis, meningoencephalitis, intraorbital or intracranial abscess, and generalized infection, such as tetanus.

According to their manner of production, we may distinguish two types of orbital stab wounds.

1. Stab wounds produced by blunt objects, such as a cow's horn, penetrating the orbit and, possibly, lacerating the eyelid. Owing to the bluntness of the stabbing object, a strong pressure is exerted on the eyeball, resulting in contusion, which may be associated with intrabulbar hematoma, rupture of the sclera, avulsion of the ciliary attachment of the iris, or luxation of the lens.

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2. Stab wounds proper, produced by long, slender, pointed objects (pitchforks, twigs, pencils, etc.), which may impinge on, but do not damage, the eyeball because it is pushed aside in the compressible fatty tissue of the orbit at the moment of injury. As the orbital fossa has the shape of a horizontal, four-sided pyramid, the impact of the injury may be led posteriorly along one of the orbital walls if the direction of the force is in the sagittal plane. Here there is easy access to the cranial cavity through the superior orbital (sphenoidal) fissure or, directly, through the thin roof of the orbit. If the direction of the impact is from below upward, as is commonly the case because of the unconscious throwing back of the head at the time of injury, the stabbing instrument may pass through the orbital cavity, fracture its roof, and lacerate the frontal lobe. In this case, injury to the orbital contents need only be minimal and, as compared with the cerebral complications, is usually negligible.

This paper is concerned with the second type only, i. e., orbital stab wounds proper. In these, the entrance wound is usually inconspicuous; local symptoms may be mild, with no, or only transient, visual disturbances, but with the possibility of intracranial complications, which may at first be masked by the ocular symptoms.

REVIEW OF LITERATURE

Orbital stab wounds have previously been described by Birch-Hirschfeld [1] (1930), who reported 172 cases (including 3 of his own).* Colley [4] (1934) reported three uncomplicated cases; in two repeated examination of the wound revealed the presence of wooden foreign bodies in the orbit. Rees [12] (1947) published a case in which a twig perforated the orbit and injured the optic nerve, the muscle cone, and the third, fourth, fifth, and sixth cranial nerves. Svoboda [14] (1948) reported a case in which a 10-year-old boy sustained an injury to the eye in a duel fought with toy swords. An orbital hematoma developed, resulting in protrusion of the eyeball. In spite of progressive papilledema, lumbar pneumoencephalography was performed through a mistake 34 days after the injury; death occurred during this procedure. Autopsy revealed that the sword point had penetrated the superior orbital fissure and the cavernous sinus. McClure and Gardner [10] (1949) reported four cases with intracranial complications, one of which terminated fatally. Neudörfer [11] (1949) published a case in which the orbital wound was inflicted by a piece of wood. For three years suppuration from the lower eyelid persisted. Exploration of the orbit was carried out repeatedly, without success, but subsequent orbitotomy revealed the presence of several splinters of wood. Ehlers [5] (1937), Field [6] (1951), Gorovaya and Vasilyeva [7] (1951), and others described cases without cerebral complications. Schneider and Henderson [13] (1952) mentioned a case of an ice pick stab in the orbit. At the first examination the lesion seemed to be uncomplicated, but in the course of a few days a number of uncharacteristic neurological manifestations developed. Craniotomy was performed, but death ensued eight days after the injury. Autopsy revealed lesions of the superior orbital fissure, the internal carotid artery, the cavernous sinus, the pons, the pyramidal tracts, and one of the cerebellar hemispheres.

As orbital stab wounds are often produced by dirty twigs, pitchforks, etc., the conditions for growth of Cl. tetani and other anaerobic bacteria are very favorable.

* Twenty of these patients died (meningitis, 11; injury of the internal carotid artery, 6, and tetanus, 3). In 125 cases there was lesion of the optic nerve.

Birch-Hirschfeld [2] surveyed 30 previously reported cases of tetanus in which a variety of orbital lesions formed the portal of entry of the infection. In 14 of these tetanus was due to lesions produced by pointed pieces of wood. Of these 30 cases, 20 terminated fatally. Castelain and Lafargue [3] (1920) collected 21 cases of facial tetanus following various ocular lesions. Another case of facial tetanus following an orbital stab wound, which is included in this series, was described by Øster [15] (1945).

Hansen [7] (1942) published three cases of slight orbital stab wounds unassociated with intracranial complications. Transitory and permanent impairment of vision, respectively, developed in two of the patients, while the third had normal visual acuity. Perimetry showed that all three patients had a defect in the field of vision. Ophthalmoscopic examination showed normal conditions immediately after the accident, whereas atrophy of the disc was revealed at the follow-up examination. It was emphasized that since impairment of vision may be of transitory character, it cannot be interpreted as a sign of a deep lesion involving the optic nerve. On the other hand, the occurrence at a later stage of defects in the field of vision, possibly accompanied by atrophy of the disc, may be regarded as definite evidence of direct or indirect involvement of the optic nerve.

TABLE I.—*Types of Stabbing Instruments*

	Adults	Children
Pitchforks	4	3
Broken twigs	2	3
Keyhole saw	1	..
Scythe point	1	..
Iron bar	..	1
Total	8	7

The stabbing objects have especially been splinters of wood, but curtain rods, toy swords, straws, broken glass, knife blades, pencils, pipestems, knitting needles, and umbrella ribs have also been reported. On the other hand, reports of stab wounds caused by pitchforks seem to be comparatively rare in the literature, although this implement shows the highest frequency in the present series. Lesions due to twigs are very dangerous because the twig breaks easily and part of it may be retained in the orbit, and serve, usually, as a source of infection.

PRESENT SERIES

Since 1943, there have been 15 patients with orbital stab wounds admitted to the State Department of Neurosurgery of Aarhus Municipal Hospital. Of these, three died, and nine patients had intracranial complications. The patients were transferred from regional hospitals because cerebral complications were suspected. Thus, the case material is selected and consists of patients with subacute orbital lesions. Of the 15 patients, 7 were children under 15 years of age.

The types of stabbing instruments are listed in Table I.

The stab wounds due to pitchforks in adults were in most cases produced during loading of peat, hay, etc., whereas the children were injured while playing with pitchforks in barns.

In three cases the manner of production of the orbital lesions due to twigs was very characteristic; in two the patient fell with a twig in his hand, while in the third

the lesion occurred during play, probably in "fencing," when the patient received a blow of a twig on his eye. That the trauma need not be very violent is seen from a fourth case, in which the orbit was pierced by a broken twig while the patient was crawling in a dark cave.

On their admission to the State Department of Neurosurgery, the conditions of the patients varied within wide limits. Slightly more than one-half presented unconsciousness, clouding of the consciousness, or aphasia, and these patients were all suffering from intracranial complications. The remaining patients were mentally unaffected. Among the latter, a case of severe intracranial lesion of the optic nerve is worthy of note.

A farm laborer (#11718), aged 16, had fallen on a pitchfork prong, which was driven into the left orbit. The patient had personally pulled the fork from the wound. Apart from loss of sight in the left eye, no immediate symptoms developed. He was taken to a local hospital immediately after the accident and was at once transferred to the State Department of Neurosurgery. On admission there the patient was alert and cooperative. A large hematoma was seen around the left eye, and below and slightly lateral to the medial corner of the eye there was a small stab wound. Slight protrusion of the left eyeball with impeded movements in all directions was noticed. The left pupil responded consensually but was fixed to light. The light sense of the eye was abolished. Ophthalmoscopic examination showed normal conditions of the eyeground. Roentgenograms of the skull, particularly of the optic foramen, did not disclose any abnormalities. Lumbar puncture revealed the presence of numerous erythrocytes in the spinal fluid. At discharge, a week later, the light sense was still abolished, but ophthalmoscopic conditions were normal. At a follow-up examination six months later, abolished light sense and absence of reaction to light persisted, but opthalmoscopic examination then revealed diffuse atrophy of the disc with no blurring of the edge. Otherwise there were no neurological abnormalities.

The patient was apparently suffering from a direct intracranial lesion of the optic nerve, since injury behind the point of entry of the central vessels would not have resulted in ophthalmoscopically demonstrable changes shortly after the trauma, and since injury at the apex of the orbit usually affects the motor nerves as well.

Among nonophthalmological manifestations on admission may be mentioned stiffness of the neck, loss of motor power, and, in one instance, spasm in the face.

In addition to hematoma of the eyelids and subconjunctival hemorrhage, ophthalmoscopical examination revealed the signs presented in Table 2.

In one patient, who had been struck in the medial corner of the eye with a scythe point, protrusion of both eyeballs, due to orbital emphysema, and epistaxis were present. As appears from Table 2, pupillary changes (anisocoria, maximal dilatation, or absence of reaction to light) were observed in seven cases.

During the hospital stay the blood pressure, pulse, and respiration were checked at regular intervals to determine any increases in the intracranial pressure. In more than one-half of the cases roentgenograms of the skull did not reveal fractures; nevertheless, in most of these cases fractures either were demonstrated at operation or, in view of other findings, such as those revealed by lumbar puncture or ophthalmoscopy, must undoubtedly have been present.

Percutaneous arteriography of the carotid artery was performed in some cases but did not provide valuable information because the intracranial hematoma or abscess was too small to produce a displacement of the vascular system.

Ventriculography, which was done in a few cases, revealed evidence of a space-occupying intracranial lesion, which was verified at operation.

Lumbar puncture was performed in slightly less than half the cases; in patients with intracranial complications abnormal conditions were revealed (increased cell counts, protein content, or xanthochromia).

Treatment.—Tetanus antitoxin and antibiotics were given in all cases. In five cases craniotomy was performed, with removal of degenerated brain tissue, hematomas, and bone splinters and, in one instance, with removal of an intracerebral abscess. In the last-mentioned case it became necessary later to remove the entire bone flap because of persistent suppuration. In four cases the wound was revised, and in one of these an embedded fragment of a twig was found, from which Cl. tetani was cultivated.

In one case enucleation had to be performed, owing to the presence of retrobulbar gas gangrene. The case history follows.

A farmer (#13308), aged 64, had had a fall with his bicycle six days prior to admission to the State Department of Neurosurgery. He struck his face against a stump of a tree, from which splinters were protruding. One of these splinters pierced the skin below the right lower lid and penetrated the orbit. Immediately after the accident the patient could see dimly with the injured eye, but loss of vision rapidly developed. There were no signs of intracranial lesion. The patient was at once taken to a local ophthalmological clinic. On admission, a large hema-

TABLE 2.—*Ocular Changes on Admission to the State Department of Neurosurgery*

	Total No. of Patients	Patients with Intracranial Lesions
Protrusion; disorders of position or movement	12	9
Pupillary changes	7	3
Papilledema	3	3
Abolished light sense	2	1
Anesthesia-analgesia of area of supraorbital nerve	2	..
Eyelid changes only	2	1

toma around the right eye, pronounced protrusion, and fixed pupil were noticed. The light sense was abolished; the eyeball was not injured. During the next few days progressive, nonpulsating protrusion of the eye and incipient necrosis of the eyelids developed. The patient was transferred to the State Department of Neurosurgery six days after the accident. Enucleation was performed. The peribulbar and retrobulbar tissue was necrotic, foul-smelling, and filled with air. Cultures from this tissue revealed the presence of Clostridium œdematiens. In spite of chemotherapy and administration of gas gangrene antitoxin, suppuration from the apex of the orbit has now persisted for three months. Renewed cultures did not yield Cl. œdematiens. Roentgenograms revealed osteitis medial to the optic foramen, and probing showed that the penetration extended to the ethmoidal cells. Three weeks after the operation two small splinters of wood were removed from the apex of the orbit. The suppuration had gradually diminished, but probably there are still some splinters left in the orbit.

A neurological examination revealed anesthesia and analgesia of the area supplied by the right supraorbital nerve. The general condition of the patient was unaffected.

Symptoms at Discharge.—The periods for which the patients stayed in the State Department of Neurosurgery varied from a few hours to 95 days; patients without intracranial complications were returned to regional hospitals at the earliest possible time. At discharge, an ophthalmological examination was carried out, and, if possible, the visual field and visual acuity were determined. The results of the examinations are shown in Tables 3 and 4.

It appears from Table 3 that vision was abnormal in two cases, that is, complete loss of sight, due to avulsion of the optic nerve in one (see above), and less than 6/6

acuity in another, in which operation had been performed for an intracranial abscess. Ophthalmoscopic examination revealed slight changes only in one case, that of a residual preretinal hemorrhage. The patients grouped under the heading "No examination" either were unable to cooperate or were discharged very early because of the absence of intracranial complications. As already mentioned, enucleation was performed in a 12th case.

In 5 of the 12 patients, neurological disorders, viz., slight aphasia, severe hemiplegia, slight paresis of the arm, and loss of sensation of touch and pain in the subcutaneous area of the supraorbital nerve, were disclosed.

Fatal Cases.—As already mentioned, three of the patients died, one of tetanus (case record published by Oster[15]) and two others of intracranial complications (edema, encephalitis). These case histories are briefly reported.

TABLE 3.—*Ocular Changes in Eleven Patients at Discharge Apart from Redness and Swelling Around the Affected Eye*

	Normal	Pathological	No Examination
Ophthalmoscopy	9	1	1
Visual acuity	5	2	4
Field of vision	5	1	5

TABLE 4.—*Additional Ocular Manifestations at Discharge*

	No. of Patients
Conjunctival changes	5
Protrusion, disorders of position and movement	5
Stricture of nasal duct	1
Ptosis	1
Fistula of eyelid	1
Suppuration from apex of orbit	1

CASE 1.—A laborer (#552), aged 20, was admitted on Jan. 18, 1944. Death occurred on Jan. 20. A twig had struck his left orbit. Disturbances of vision and headache developed at once, and the next day there was swelling around the left eye. He was then admitted to a local hospital. Five days after the accident signs of incipient tetanus with trismus were noticed, followed gradually by difficulty in swallowing, convulsions, peripheral facial paresis, and hypesthesia in the left side of the face. The patient was transferred to the State Department of Neurosurgery a week after the accident. On admission, stiffness of the neck with intermittent right-sided facial spasm, trismus, and opisthotonos was noticed. The left lower eyelid was swollen, and considerable chemosis was present. There was protrusion of the eyeball with abnormal position and decreased range of movement. Examination of the wound revealed the presence of a fragment of a twig embedded in the orbital contents at the apex. Death occurred on the day following the operation. Autopsy was uncontributory. Cultures from the fragment of the twig yielded Cl. tetani.

CASE 2.—A laborer (#11647), aged 46, was admitted on Aug. 24, 1952. Death occurred on Aug. 27. While engaged in loading a peat cart, he had been struck in the right orbit by a peat fork. He was rendered unconscious by the blow and was at once admitted to a local hospital, and three days later transferred to the State Department of Neurosurgery. On admission there, the patient was in a poor condition, with fever, clouded consciousness, stiffness of the neck, and weakness of the left lower portion of the face. On the right eyelid there was a contusion, 3 cm. in length, with a penetrating wound. There was protrusion of the right eyeball, which was dis-

placed, immobile, and somewhat injected. Pupillary conditions were normal. The patient could count fingers in front of the eye. Owing to blurring of the cornea, the right eye could not be examined with the opthalmoscope; on the left side there was slight blurring of the disc with mild venous engorgement and a few hemorrhages at the margin. A roentgenogram of the skull showed a slight, splintered fracture of the roof of the right orbit. A lumbar puncture revealed increased pressure and blood-stained spinal fluid with increased protein content. Cultures yielded negative results. Arteriography showed incomplete filling of the area supplied by the anterior cerebral artery; otherwise there was nothing abnormal. As the patient was believed to have a brain lesion in the vicinity of the third ventricle, further procedures were omitted. The patient deteriorated rapidly and died in hyperthermia three days after admission. Autopsy of the brain, performed by Dr. Erna Christensen, showed pronounced cerebral edema. The stab wound could be followed from the undersurface of the right frontal lobe into the left hemisphere, where the entire anterior end of the caudate nucleus was hemorrhagic. The left internal capsule, lentiform nucleus, and hypothalamus were also damaged. The track continued across the corpus callosum to the cortex. In the track in the frontal lobe there was a hematoma, 3.5 by 1 cm., and the surrounding tissue showed purulent encephalitis.

Case 3.—A boy (#12584), aged 3 years, was admitted on March 10, 1953. Death occurred on March 11. While playing, the patient fell in the street. The police was later informed that the boy had held a peg, the thickness of a pencil, in his hand and that this peg was driven into the right orbit and at once removed by the boy. He did not lose consciousness. The boy was at once seen by the family doctor, who treated the wound and sent the patient home, as the child was alert and apparently in good condition. A few hours later clouding of consciousness and vomiting developed. About 20 hours later the patient was again seen by the family doctor. At that time, the child was mildly somnolent but responded rationally to questions. Twenty-five hours after the accident generalized clonic spasm developed, followed by unconsciousness for about 10 minutes. Half an hour later the attack recurred. The patient was then admitted to a local hospital, from which he was transferred to the State Department of Neurosurgery a few hours later. On admission there, the patient had a high fever and was almost comatose, responding to painful stimuli only. Slight stiffness of the neck was noticed. In the right upper lid just under the orbital margin there was a small stab wound, from which cerebrospinal fluid and lacerated brain tissue was evacuated. The eyelids were markedly distended by edema and a hematoma. No ocular lesion; normal ophthalmoscopy; pupils submaximally dilated and fixed to light. No pareses of the face or extremities, but the right arm and leg moved less than their fellow members. During the examination intermittent "brain-stem fits" developed, with spasm in pronation-extension of the right arm and constant pronounced spasm in extension in both legs, especially on the right side, with a bilateral Babinski response. Roentgenograms of the skull did not reveal definite signs of fracture. Immediately on admission, a rise in the blood pressure from 135 to 210 mm., an increase in the pulse rate to 140, and embarrassed, superficial respiration with marked cyanosis developed, indicating a severe and sudden aggravation of the herniation of the brain stem through the tentorial incisure. A burr hole was at once made in the vicinity of the coronal suture, and the right anterior horn was tapped, after which fluid was emitted under excessive pressure. After this procedure consciousness returned; the blood pressure fell to 100, and the respirations became regular. Craniotomy was made, exposing the anterior part of the right hemisphere. A perforation in the middle of the roof of the orbit was revealed, together with a small circular laceration of the dura and a large hematoma in the basal part of the frontal lobe, extending across the midline into the left hemisphere and, possibly, into the third ventricle. The hematoma was removed. Shortly after the operation the patient was awake and responded rationally to questions. During the next few hours hyperpyrexia and clouding of the consciousness developed. Repeated tapping of the right anterior horn and intravenous administration of 50% dextrose solution proved ineffective. Clonic spasm, of gradual onset, of the extremities on the left side developed. Death ensued the next day. Autopsy, performed by Prof. W. Munck, revealed the course of the track of the stabbing object. It was about 1 cm. in diameter and ran from the opening of the perforation in the roof of the orbit in an oblique superoposterior direction through the right frontal lobe into the third ventricle. The entire length of the track from the external wound was about 8 cm. Pronounced cerebral edema, purulent leptomeningitis, and phlegmon of the orbital tissue were disclosed.

Follow-Up Examinations.—All 12 patients returned for follow-up examination 2 months to 10 years after discharge from the State Department of Neurosurgery. In all cases an ophthalmological examination was made, comprising ophthalmoscopy and determination of visual fields and visual acuity. Most of the patients were also subjected to a neurological examination.

According to the patients' own statements, the condition since discharge had been as summarized in Table 5.

The mental changes referred to in Table 5 were impaired memory, irritability, and erethism.

The physical and neurological examinations gave the findings stated in Table 6.

TABLE 5.—*Condition Since Discharge*

	Total No. of Patients	No. of Patients with Intracranial Complications
No complaints	2	2
Mental changes	4	4
Periods of headache	3	1
Convulsive seizures	1	1
Loss of sight in one eye	2	1
Hemiparesis	1	1
Symptoms of stricture of nasal duct	1	..
Persistent suppuration from orbit	1	..
Transitory suppuration from wound	1	..
Unilateral paresthesias in frontal region	2	..

TABLE 6.—*Objective Findings at Follow-Up Examination*

	No. of Patients
Pareses and reflex changes	3
Slight aphasia and epileptoid mental changes	1
General mental blunting	4
Bone defect after craniotomy	1
Hypesthesia-hypalgesia of area of supraorbital nerve	2
Obesity	1
Normal conditions	5

All the patients had regained full working capacity, but four showed general mental blunting. Although the pretraumatic mental state of these patients was not known, there seemed to be a direct relationship to the intracranial lesion in three cases. Of the three patients with pareses mentioned in Table 6, one had a slight spastic hemiparesis and staggering gait; the other two had only weakness of the right arm and of the lower face, respectively, and reflex changes in the form of a unilateral atypical plantar reflex and right-sided exaggeration of the deep reflexes.

The results of the ophthalmological examination appear in Table 7.

Visual fields and visual acuity and ophthalmoscopic conditions were normal in all patients with the exception of the two with lesions of the optic nerve and sequelae of enucleation.

Changes in the position of the eyeball were measured with Hertel's exophthalmometer.

The case history of the patient with obesity mentioned in Table 6 deserves brief mention.

A boy (#2823), aged 6 years, had, while playing, the prong of a fork driven through the left upper eyelid. He fainted at once. After return of consciousness he was somnolent, and fever developed. He was at once admitted to a local hospital and 12 days later transferred to the State Department of Neurosurgery. On admission there, stiffness of the neck and somnolence were noticed. The left eyelid was swollen, and there was slight protrusion of the eyeball, which was turned downward. An ophthalmoscopic examination showed papilledema, particularly of the left eye, yet without measurable prominence. A roentgenogram did not reveal any abnormalities of the roof of the orbit. Placement of a burr hole with probing in the frontal lobe did not give any result. Ventriculography six days later showed upward displacement of the left anterior horn. Subsequent craniotomy revealed a hematoma, the size of a walnut, in the basal part of the frontal lobe and extending across the midline. Removal of the hematoma was followed by gradual improvement of the condition. An ophthalmological examination before discharge showed that the patient was able to count fingers at 6 meters. Ophthalmoscopy revealed normal conditions except for a disappearing preretinal hemorrhage. At a follow-up examination six years later there were no complaints, but the patient had gained weight very rapidly during the previous year.

TABLE 7.—*Ophthalmological Findings at Follow-Up Examination*

	No. of Patients
Sequelae of enucleation with suppuration from apex of orbit	1
Moderate enophthalmos	2
Moderate protrusion	1
Moderate divergence of one eye	1
Ptosis	1
Atrophy of optic disk with loss of sight	1
Stricture of nasal duct	1
Corneal hypesthesia	1
Normal conditions	6

Ophthalmological and neurological examinations showed a normal condition. The patient was mentally retarded.

The obesity observed could scarcely be ascribed to the lesion of the mesial areas of the frontal lobes, since it did not develop until after the lapse of five years and seemed to be related to changes in the dietary habits of the home, which had also resulted in considerable weight gains in the other members of the family. Nor, it would seem, is it reasonable to assume that the mental retardation was an immediate consequence of the head injury, since both parents and the remaining children of the family were all mentally retarded.

COMMENT

The series presented, consisting of 15 patients, of whom 3 died and 9 had intracranial complications, is a selected one in that they were chiefly cerebral cases transferred to the State Department of Neurosurgery.

Among the nine patients suspected of intracranial complications on admission, three did not show signs of such disorders immediately after the injury. This illustrates how easily an intracranial lesion may escape recognition. That signs of such complications are liable to be overlooked appears from the fact that four patients were not transferred to this hospital until 3 to 25 days after the accident, although these patients had exhibited signs of cerebral complications, such as loss of consciousness followed by states of clouding or aphasia, immediately after the trauma.

On the other hand, the patient with tetanus was transferred a week after the accident because thrombosis of the cavernous sinus or subdural hematoma was suspected. As previously pointed out, negative x-ray findings do not preclude the presence of orbital fracture. Spinal fluid examination is apparently a fairly safe method for the confirmation of intracranial hemorrhage or infection. However, owing to the risk of tentorial incarceration, it should be used only in the absence of increased intracranial pressure.

Even though a demonstrable change in the position or movements of the eyeball is usually due to a retrobulbar hematoma or injury to muscles or nerves, it should be borne in mind that it may also be due to an embedded foreign body, traumatic emphysema, gas gangrene, thrombosis of the cavernous sinus, or an aneurysm or edema of the orbital tissue. Pupillary changes and impairment of vision may be due to cerebral complications, but may also be caused by compression of the eyeball at the moment of injury or by a retrobulbar hematoma. In contrast with the three cases of orbital stab wounds described by Hansen,* who found a direct or an indirect lesion of the optic nerve (hemorrhage into the sheath of the optic nerve, periosteal thickening, and callus formation, respectively) evidenced in all three by changes in the visual field and subsequent atrophy of the disc, the present series showed a lesion of the optic nerve only in one case, that of a severe, direct lesion of the nerve without demonstrable ophthalmoscopic changes immediately after the accident, but with well-defined atrophy of the disc six months later (see above).

As previously emphasized, in contrast to blunt objects, gunshots, etc., pointed instruments may push the eyeball aside at the time of injury without causing damage to it. In agreement with this, in none of the cases in the present series of stab wounds proper was there injury of the eyeball.

At the follow-up examination, the visual field and visual acuity were found to be normal except in the two cases with injury of the optic nerve and sequelae of the enucleation, respectively. On the other hand, the sequelae of the cerebral complications were far more serious; two patients died, and, as it appears from Tables 5 and 6, it is reasonable to assume that these complications resulted in general mental blunting in three cases, with slight aphasia in one, slight pareses in two, and epilepsy in one.

SUMMARY

Fifteen cases of orbital stab wounds, including 7 in children, are analyzed. In seven cases the lesion was caused by a pitchfork, while in the remaining eight it was due to twigs, a keyhole saw, an iron bar, and a scythe point. Intracranial complications occurred in nine cases, and tetanus and gas gangrene each developed in one case, in which splinters of wood were retained in the orbit. The patient with tetanus and two of those with intracranial complications died. The eyeball was not injured in any of the cases, but enucleation was performed in one case, because of retrobulbar gas gangrene and monstrous protrusion. The symptoms, differential diagnosis, and treatment are discussed. At the follow-up examination, all the patients had regained full working capacity, but four had various permanent cerebral symptoms, such as general mental blunting, slight aphasia, slight loss of motor power, and convulsive seizures.

Ophthalmoscopic conditions, visual acuity, and the field of vision were normal in all but two cases; in one of these, a direct lesion of the optic nerve had occurred,

and in the second enucleation had been performed. It is emphasized that local symptoms may be slight in orbital stab wounds and that the injury should never be regarded as an isolated ocular lesion, even if cerebral symptoms are absent immediately after the trauma.

CONCLUSIONS

Patients who have sustained injury to the orbit should at once be admitted to a hospital, since both orbital and/or cerebral symptoms may be slight or absent immediately after the trauma. Roentgenograms of the orbital region should be taken, and during the hospitalization the patient should be closely observed for intracranial complications. The blood pressure, pulse, respiration, and temperature should be checked regularly; the spinal fluid may under certain circumstances be examined, and special attention should be paid to neurological disorders, such as loss of power, aphasia, and mental clouding. The patient should be transferred to a neurosurgical hospital if signs of cerebral complications, such as clouding of the consciousness, increased intracranial pressure, or localized motor and sensory disorders, develop.

It cannot be too strongly impressed on parents that children's playing with pitchforks, shooting with bow and arrows, and fencing with toy swords involves a great risk of orbital stab wounds and their serious consequences.

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EXPERIMENTAL EXOPHTHALMOS PRODUCED BY CORTISONE IN RATS

Further Observations

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THE OBSERVATION that rats given cortisone for a prolonged period of time became "exophthalmic"[1] prompted several questions. Was it, first of all, justifiable to consider the changed appearance as being due to classical exophthalmos, i. e., the undue protrusion of eyeballs normal in size and shape owing to changes in the retrobulbar tissues of the orbit; or was this appearance caused by a hormonally induced enlargement of the eyeballs, so that the latter no longer could be accommodated by the orbit? The second possibility was not considered likely on anatomical grounds. On the other hand, Jackson[2] had observed that the eyeballs in chronically undernourished rats continued to grow, although any gain in body weight was prevented by the restriction of food intake. Since the prolonged administration of cortisone produces in rats a state not unlike chronic inanition, it was decided to examine the effect of this hormone on the weight of the eyeballs of the growing rat.

Another aspect of experimental exophthalmos which was investigated in the experiments described in this paper is the part played by the thyroid-stimulating hormone of the adenohypophysis in the production of exophthalmos. Many workers consider that this sign is due to the excessive production of thyroid-stimulating hormone by the pituitary, mainly because ocular protrusion can be induced experimentally by the injection of pituitary extracts containing the thyroid-stimulating hormone.[3] Its occurrence in animals after treatment with cortisone alone raised the question whether proptosis could also be produced by the hormone in the absence of thyroid-stimulating hormone, and suggested a study of the ocular effects of cortisone in the hypophysectomized rat.

Clinicians have been aware for some time of the beneficial effects of thyroid hormone in the treatment of some cases of exophthalmos; the explanation given was based on the inhibition of the pituitary production of thyroid-stimulating hormone by the administered thyroid hormone. As an alternative explanation, it is suggested that the favorable effect of the thyroid hormone is due to the increased utilization of the excess of adrenal steroids. If this hypothesis is correct, it should be possible to abolish or prevent the exophthalmos due to cortisone by the induction of a hyperthyroid state of increasing severity.

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METHODS

Three separate experiments were undertaken. They are part of an investigation on the effects of prolonged treatment with cortisone on the growth of weanling male rats which will be reported in detail elsewhere.

Experiment 1.—This experiment was designed to study the effects of cortisone and of the thyroid hormone, given either singly or combined, on the weight of the eyeballs of rats fed dietary supplements of fat or liver extract. Eighty-eight male weanling Wistar albino rats weighing 45 to 55 gm. at the start of the experiment were divided into 16 groups of 5 to 6 rats each (Table 1; Fig. 1). They were offered ad lib. a fat-free diet (Groups I, II, V, and VI), which in some groups (Groups III, VII, VIII, and XIV to XVI) was supplemented with 3% of fat or with 10% of dessicated fat-extracted liver (Groups IX to XII). Some animals of these three major dietary groups were given, in addition, 0.05, 0.1, or 0.2% of desiccated thyroid powder (thyroid U.S.P.) mixed with the food and/or were injected subcutaneously with 1.5 mg. of cortisone acetate (Cortone, diluted with saline to 0.1 ml.) daily for six days a week for four weeks. Each rat therefore received a total of 36 mg. of cortisone. Since the administration of cortisone and of the thyroid hormone led to a marked impairment of growth, four additional groups of six rats each (Groups A to D) were given the basic diet with the supplement of fat and were killed when they had reached the average weight of 65, 82, 85, and 102 gm., respectively. They represent the weight controls for this experiment. All the other animals were killed on the 29th day of the experiment.

Experiment 2.—In this experiment the effect of the prolonged administration of cortisone on the eyeballs of the hypophysectomized animal was studied. Thirty-five male rats were hypophysectomized when they reached the weight of 50 to 84 gm., average weight 66 gm., and the following day the experiment was begun. The animals were fed ad lib. the basic diet supplemented with 10% of liver powder and 10% of fat, a ration which ensures good growth in normal animals, and were offered the choice of tap water and 0.9% sodium chloride solution. Seventeen of these animals were treated with cortisone in the manner and dosage described in the previous experiment (Group HyC; Table 1, Fig. 1); the rest were kept as controls (Group Hy; Table 1, Fig. 1). Death was brought about after the 28th day. The completeness of the hypophysectomy was checked by inspection of the pituitary fossa with a magnifying glass and confirmed by the organ weights, notably the weight of the testicles and the adrenals.

The effects of varying degrees of hyperthyroidism on the weight of the eyeballs and on the appearance of the animal were studied in Experiment 3, in which 64 male rats of an inbred strain from this laboratory, weighing 45 to 55 gm. at the start of the experiment, were used. They were divided into three major groups which received 0.4%, 0.2%, or no thyroid U.S.P. mixed into the basic diet of Experiment 1, to which a supplement of fat had been added (3%). Each of these three major groups was subdivided into two groups of 10 to 12 rats, of which 1 was treated with cortisone (Groups 2, 4, 6; Table 2). The dose per animal was 1.25 mg. of cortisone acetate (Cortone Acetate) given subcutaneously six days a week for five weeks, so that each rat received a total of 37.50 mg. of cortisone acetate. The experiment was terminated on the 35th day.

All the animals were weighed on the day of autopsy and were killed by exsanguination under light ether anesthesia. Both eyeballs were rapidly removed, trimmed, and weighed to the nearest milligram. The figures presented in this paper refer either to the average weight of both eyeballs of all the animals in one group, expressed in milligrams (absolute eyeball weight), or to the average eyeball weight, in milligrams per 100 gm. of body weight (relative eyeball weight).

RESULTS

EXPERIMENT 1.—*The Effect of Cortisone and/or Thyroid Hormone on Eyeball Weights of Intact Rats.*—The data for this experiment are summarized in Table 1 and in Figure 1. The lack of fatty acids in the diet produced a significant ($P < 0.05$) inhibition of the growth of the body and of the eyeballs (Group I), which was counteracted by the supplement of fat (Group III), but not of liver (Group IX). The favorable effect of fat on the growth of the eyeball could still be

seen when a mild degree of hyperthyroidism was induced by feeding the rats 0.05% of thyroid U. S. P. (Groups V, VII, and XI). But whereas in the mildly hyperthyroid animal the absolute weight of the eyeballs was not significantly different from that of the euthyroid controls, an increase in the severity of the hyperthyroid state, caused by raising the level of thyroid fed to 0.1 or 0.2% (Groups XV, XVI), led to a progressive decrease of the eyeball weights. Owing to the propor-

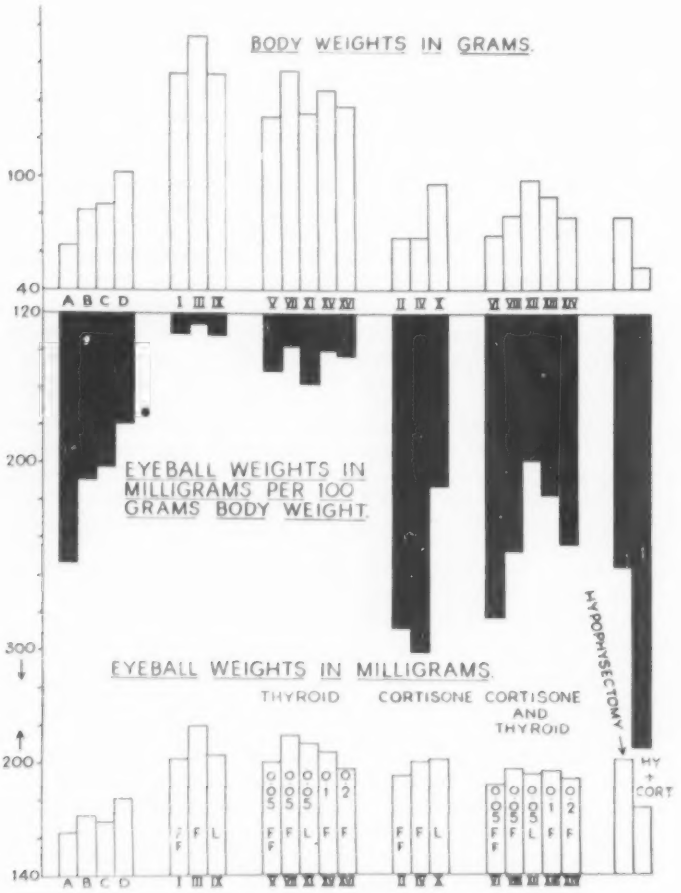

Fig. 1.—Absolute and relative eyeball weights of rats treated with cortisone and with thyroid hormone.

tionate loss of body weight, however, the ratio of eyeball weight to body weight remained constant in the groups of rats given supplements of fat; this is in contrast to the significant increase of this ratio when thyroid was fed to animals on the fat-free diets.

The marked inhibition of body growth caused by treatment with cortisone was not accompanied by a proportionate change in the weight of the eyeballs. In animals

on the fat-free diets, for example, cortisone had no obvious effect on the eyeball weight (Groups II and X), but when it was given to rats receiving the supplements of fat (Group IV), a significant ($P < 0.05$) reduction in the weight of the eyeballs, as compared with that of the normal controls, was found. The favorable effect of supplements of fat on the growth of the eyeball is apparently suppressed by the induction of a hypercorticoid state.

Attention should be drawn to the striking increase in the relative eyeball weights of animals treated with cortisone, the result of the disproportionate inhibition of

TABLE 1.—*Effect of Cortisone and of Thyroid Hormone on the Eyeball Weights of Rats Fed Various Dietary Supplements*

Group	Thyroid U. S. P., %	Cortisone, 1.5 Mg./Day	Fat, 400 Mg./Day	Desiccated Liver, 10%	No. of Rats	Body Weight, Gm.	Eyeball Weight, Mg.	Eyeball Weight, Mg./100 Gm. Body Weight
I	—	—	—	—	5	155 ± 2.4	202 ± 4.4	131 ± 2.8
III	—	—	+	—	5	175 ± 5.8	219 ± 4.2	126 ± 5.9
IX	—	—	—	+	5	155 ± 3.8	204 ± 2.9	132 ± 3.2
V	0.05	—	—	—	5	132 ± 2.6	200 ± 5.0	151 ± 2.9
VII	0.05	—	+	—	4	157 ± 9.5	214 ± 2.3	138 ± 7.0
XI	0.05	—	—	+	4	134 ± 7.5	210 ± 2.6	158 ± 7.0
II	—	+	—	—	5	68 ± 4.6	193 ± 1.2	288 ± 19.2
IV	—	+	+	—	4	68 ± 5.8	260 ± 6.1	301 ± 29.4
X	—	+	—	+	4	97 ± 7.7	201 ± 5.9	212 ± 13.4
VI	0.05	+	—	—	5	69 ± 5.9	188 ± 1.6	282 ± 22.5
VIII	0.05	+	+	—	4	80 ± 4.9	196 ± 3.1	247 ± 14.3
XII	0.05	+	—	+	3	99 ± 8.1	194 ± 3.8	198 ± 12.5
XIII	0.10	+	+	—	3	90 ± 4.7	195 ± 7.5	218 ± 3.2
XIV	0.20	+	+	—	3	79 ± 3.5	191 ± 6.2	243 ± 12.3
XV	0.10	—	+	—	5	147 ± 3.4	206 ± 3.4	140 ± 3.4
XVI	0.20	—	+	—	3	138 ± 3.6	197 ± 3.9	143 ± 2.0
				Weight Controls				
A	—	—	+	—	6	64 ± 0.8	163 ± 2.5	253 ± 5.4
B	—	—	+	—	6	84 ± 2.1	170 ± 1.3	205 ± 5.6
C	—	—	+	—	6			
D	—	—	+	—	6	102 ± 2.5	181 ± 2.0	179 ± 5.4
				Hypophysectomized Rats				
Hy	—	—	10%	+	6	79 ± 2.4	201 ± 4.1	255 ± 11.4
HyC*	—	+	10%	+	9	52 ± 4.2	176 ± 4.1	351 ± 22.3

body growth caused by this hormone (Groups II, IV, and X). Owing to the significantly ($P < 0.01$) better growth of animals fed suplements of liver extract (Group X) than of the rats on the fat-free diet with or without additional fat (Groups II and IV), the increase of the relative eyeball weights was least pronounced in that group. This is considered to be another example of the favorable effect of liver on the manifestations of hypercorticism.*

An unexpected finding emerged when cortisone was given to animals fed thyroid. Whereas neither of these hormones given separately (Groups II and V) had a significant effect on the weight of the eyeballs of rats fed the fat-free diet, their combined administration (Group VI) produced the lowest eyeball weights of the whole

* Reference 4. Greenberg, S. M., and Aterman, K., paper in preparation.

series. No explanation of this effect can be given. It is in contrast to the lack of effect of this combination of hormones on the absolute eyeball weights of animals receiving the supplements of fat as well (Groups VIII, XIII, and XIV), which remained remarkably constant; by comparison with animals given cortisone alone, the relative eyeball weights were significantly lower.

It is apparent from Table 1 that the relative eyeball weights of all animals treated with cortisone, irrespective of any other treatment given, were high. In many of these animals exophthalmos developed at some stage of the experiment; this curious association would at first sight suggest a disproportionate growth of the eyeballs as an explanation of the occurrence of ocular protrusion. Detailed comparison in individual animals of the absolute and relative eyeball weights with the incidence and degree of proptosis did not, however, support this conclusion. The highest relative eyeball weights, for instance, were occasionally found in rats with no or only transient exophthalmos; conversely, the marked fluctuations of the figures for the relative eyeball weights in different treatment groups were not accompanied by similar differences in the state of the eyes of the animals concerned.

The growth of the eyeballs of all these experimental animals was compared with the eyeball weights of untreated, young controls of similar average body weights (Group A to D). Although the absolute eyeball weights of the latter were significantly lower (Table 1; Fig. 1), the relative eyeball weights in control group A exceeded those of some groups of rats treated with cortisone; they were not accompanied by the occurrence of ocular proptosis.

Experiment 2.—*Effect of Cortisone on Eyeball Weights of Hypophysectomized Animals.*—Despite hypophysectomy, the eyeballs continued to grow (Group Hy; Table 1, Fig. 1). This result confirms the experiment of Walker, Simpson, Asling, and Evans,[5] who found that the eyeballs of rats hypophysectomized at 6 and at 28 days of age reached virtually normal weights after 60 days. They noticed that the relative eyeball weights of these animals were disproportionately large, but they did not mention the occurrence of exophthalmos. Exophthalmos was not observed, despite careful inspection, in rats of the experimental series reported here, although their relative eyeball weights equaled or exceeded those of intact animals treated with cortisone, in which ocular protusion did occur.

The administration of cortisone to hypophysectomized rats (Group HyC; Table 1, Fig. 1) produced a significant ($P < 0.01$) reduction of both the body weights and the eyeball weights; their ratios were the highest recorded for the whole experiment. Nevertheless, exophthalmos was not seen in any animal of this group throughout the period of cortisone administration.

Experiment 3.—*Effect of Increasing Doses of Thyroid Hormone on Ocular Protrusion Produced by Cortisone.*—The results of this experiment, summarized in Table 2, confirmed some of the observations on the effects of the increasing severity of the hyperthyroid state on the absolute and relative eyeball weights reported in Experiment 1 of this paper. It is apparent that a significant inhibition of the growth of the body and a proportionate reduction of the weight of the eyeballs resulted from the severe hyperthyroidism produced by feeding 0.4% thyroid U. S. P. to the rats for five weeks (Group 5). The relative eyeball weights, however, did not undergo any gross changes. Cortisone, on the other hand, not only produced

a significant decrease in the weight of the eyeballs, but, owing to the marked stunting of the growth of the body, caused the ratio of the eyeball weight to body weight to rise considerably (Group 2). When, however, cortisone was given to animals fed the thyroid, the effects of these two hormones opposed each other to a certain extent (Groups 4 and 6). It can be seen, for instance, that the inhibition of body growth produced by giving cortisone alone was significantly reduced by feeding 0.2 and 0.4% of thyroid as well, as was the marked increase in the relative eyeball weights. Although there were present significant differences in the body weights of animals in these groups, a significant linear regression was not obtained. The rats treated with cortisone grew better if they were fed the diet containing 0.2% of thyroid than if the diet contained either 0.4% or no thyroid at all. This, presum-

TABLE 2.—*Average Eyeball Weights of Rats Treated with Cortisone and with Increasing Amounts of Thyroid*

Group	Cortisone, 1.25 Mg./Day, 6 Days/Wk., 5 Wk.	Thyroid U. S. P. Added to Diet	No. of Animals	Body Weights, Gm.	Eyeball Weights, Mg.	Ratio of Eyeball Weights to Body Weights (Mg./100 Gm.)
1	—	—	6	164 ± 10.71	222 ± 3.87	137 ± 9.53
2	+	—	9	98 ± 5.83	203 ± 1.73	215 ± 14.01
3	—	0.2%	7	176 ± 9.21	217 ± 2.77	125 ± 6.86
4	+	0.2%	9	123 ± 6.17	204 ± 2.80	168 ± 7.28
5	—	0.4%	10	133 ± 7.66	202 ± 2.76	157 ± 6.37
6	+	0.4%	5	107 ± 3.65	194 ± 1.43	182 ± 5.84

TABLE 3.—*Incidence of Exophthalmos in Rats Treated for Five Weeks with Cortisone and with Increasing Amounts of Thyroid*

Treatment		No. of Animals in Which Exophthalmos Was					
		Present		Doubtful		Absent	
				Observer			
Cortisone	Thyroid U. S. P.	K. A.	S. G.	K. A.	S. G.	K. A.	S. G.
1.25 mg./day	.....	6	4	3	4	1	2
1.25 mg./day	0.2%	0	0	4	4	5	5
1.25 mg./day	0.4%	0	0	1	3	4	2

ably, means that there exists a certain optimal concentration of both these hormones, at which their mutually opposing effects are best seen. A disturbance of this "equilibrium" by allowing either hormone to predominate, by giving cortisone either without any thyroid (Group 2) or with too much of it (Group 6), produces the typical signs of hypercorticism or hyperthyroidism; the occurrence of the latter explains, for instance, the significant difference in the body weight between animals given 0.2% and animals given 0.4% of powdered thyroid in the presence of the same amount of cortisone injected. The same interpretation presumably applies to the data for the eyeball weights; the significant linear regression found if the amount of thyroid fed to the animals was raised was no longer present if this was combined with the administration of cortisone.

All the animals of these six groups were studied throughout the duration of the experiment for signs of ocular protrusion. In only a few of the rats not receiv-

ing cortisone was there a suspicion of proptosis. When definite exophthalmos was seen, it was observed only in rats treated with cortisone. Its incidence was highest in the first three weeks of the experiment and tended to decrease with time. This trend was particularly marked in animals receiving the thyroid as well as cortisone, in which daily observation revealed a definite tendency for the proptosis to diminish as the severity of the hyperthyroidism increased; in the group of rats ingesting the highest level of thyroid (0.4%, Group 6), it was difficult to be certain whether any ocular protrusion at all had been produced by cortisone. Table 3 shows that shortly before autopsy, after five weeks of treatment, the diagnosis of exophthalmos could be made with certainty only in animals treated with cortisone alone, but became doubtful if they were treated with high levels of thyroid as well (Fig. 2).

COMMENT

Addis, Poo, and Lew [6] have shown that the eyeballs of the rat, as distinct from some other organs, do not participate in the loss of body weight brought about by a seven-day fast. Although the various treatments described in the present experiment did produce a marked inhibition of body growth, this was reflected only to a comparatively slight degree in the eyeball weights of these animals; the severe dwarfing of the body caused by cortisone, for instance, did not lead to any greater reduction in the weight of the eyeballs than did the comparatively mild inhibition of body growth which occurs if the growing rat is fed a diet lacking in essential fatty acids. The continued growth of the eyeballs despite the severe disturbance of the body growth following hypophysectomy, hyperthyroidism, or hypercorticism recalls similar observations by Jackson [2] on rats the body weights of which were kept constant throughout the experiment by chronic underfeeding; by Walker and associates [5] on rats hypophysectomized at an early age, and by Scow and Simpson [7] in newly born thyroidectomized animals.

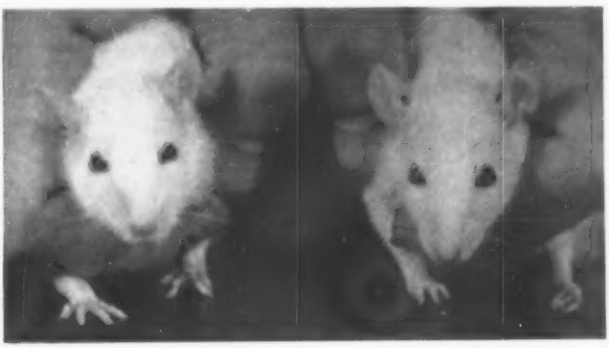

Fig. 2.—Effect of thyroid hormone on the exophthalmos induced by cortisone. The animal on the right developed definite exophthalmos after two weeks' treatment with cortisone (1.25 mg. a day, six days a week). Ocular protrusion is absent in the control animal (left), treated with cortisone and given 0.4% of the thyroid U.S.P. in the diet as well.

It has already been pointed out that ocular protrusion could be observed only in animals that were treated with cortisone. The constant occurrence of a significant increase in the relative eyeball weights in these animals would at first suggest that

the appearance of exophthalmos was caused by, or connected with, the disproportion between the continued growth of the eyeball and the stunting of the rest of the body. However, neither the relevant data on individual animals nor those on animals belonging to the various other groups described here support this inference. Exophthalmos, for example, was absent in hypophysectomized rats despite treatment with cortisone, although theirs were the highest relative eyeball weights of the whole series; but it was present in intact animals treated with cortisone, although their relative eyeball weights were lower than those of some untreated young controls in which ocular protrusion was never seen. Neither Walker and associates [5] nor Scow and Simpson,[7] who drew attention to the marked increase in the relative weight of the eyeballs in hypophysectomized or thyroidectomized rats, mentioned the occurrence of exophthalmos in experimental animals. It is, therefore, considered to be unlikely that the cause of ocular protrusion will be found in the disproportionate growth of the eyeballs relative to the rest of the body; nor can it be accounted for by an absolute enlargement of these structures, as had already been shown by Smelser [8] for the guinea pig, and by Sellers and Ferguson [9] for rats treated with propylthiouracil. In view of the occurrence of ocular protrusion in rats with normal or smaller than normal eyeballs, the possibility cannot be ruled out that the exophthalmos induced by cortisone depends on changes in the retrobulbar tissues similar to those demonstrated by Smelser [8] as the cause of experimental exophthalmos in guinea pigs.

It is unlikely that the failure of hypophysectomized animals to develop ocular protrusion in spite of treatment with cortisone could be explained by the dose of cortisone not being adequate, since both the weight of the body and the weight of the thymus showed a significant reduction by comparison with those for hypophysectomized controls. It is suggested that marked exophthalmos is the result of a synergistic effect of an excess over current metabolic requirements of adrenal steroids and of a normal or raised level of thyrotropin. The experiments reported here lend support to this suggestion; in the absence of thyroid-stimulating hormone an excess of cortisone alone cannot cause exophthalmos. This view bears a certain similarity to the conclusion of Levin and Farber [10] that the ability of an animal to mobilize fat from the depots to the liver requires at least two factors, namely, adequate supplies of adrenocortical steroids and an unidentified "triggering" factor derived from the adenohypophysis. In support of the conclusion of these workers, the daily administration of 1.5 mg. of cortisone to immature hypophysectomized rats in this experiment had no effect whatever on the level of liver fat as measured at autopsy, for at that time the wet liver fat of the hypophysectomized rats (6) was (including the standard error of the mean) $4.84 \pm 0.29\%$, while that of the hypophysectomized-cortisone-treated rats (7) was $4.73 \pm 0.31\%$. It should be pointed out in this connection that the production of exophthalmos in experimental animals is often accompanied by a stimulation of fat metabolism and the occurrence of fatty livers.†

The well-known clinical observation of the favorable effect of treatment with thyroid hormone on the course of endocrine exophthalmos is borne out by the findings of the present experiments. The mechanism by which the thyroid hormone produces this effect is not quite clear; it appears, however, that one of the impor-

† References 11 through 14. Greenberg, S. M., and Aterman, K., paper in preparation.

tant factors is the amount of the hormone fed the animal. Whereas the ingestion of comparatively small amounts (0.5-0.1%) over the period given had little effect on the incidence or the degree of exophthalmos produced by cortisone, its inhibiting effect became pronounced when the amount of thyroid fed was raised to 0.2 or 0.4%. It is unlikely that the differences in the incidence of exophthalmos in rats treated with cortisone with or without added high levels of thyroid hormone can be accounted for merely by the relatively small differences in the weights of the eyeballs and the bodies of these animals; it is more probable that the dependence of the ocular protrusion caused by cortisone on the severity of the hyperthyroid state induced at the same time is merely another expression of the well-known antagonism between the effects of the hormone of the thyroid gland and those of the adrenal cortex. The findings presented here, although they do not prove it, are compatible with the suggestion that the favorable effect of the thyroid hormone on the degree of ocular protrusion is determined by the rise in the metabolic rate of the animal, which the administration of thyroid hormone must cause; this, in turn, leads to increased requirements and to a more rapid utilization of adrenal steroids, an excess of which either can no longer be built up or is rapidly reduced.[15] Thus, one of the factors essential for the production of exophthalmos is removed, and proptosis is either prevented or significantly decreased.

SUMMARY

The growth of the eyeballs of male weaning albino rats was studied under various hormonal and dietary conditions. A diet lacking in essential fatty acids produced a significant reduction of the eyeball weight. Despite a severe inhibition of body growth in hypophysectomized, hypercorticoid, or hyperthyroid rats, the eyeballs continued to grow. Although cortisone in intact animals regularly produced ocular protrusion, it had no such effect in hypophysectomized rats. The ocular proptosis induced by cortisone was not dependent on an increase in the absolute or relative eyeball weights but was significantly inhibited if a severe degree of hyperthyroidism was induced at the same time. It is suggested that the thyroid hormone produces this effect on ocular protrusion by preventing the building up of an excess of adrenocortical steroids.

Dr. Elmer Alpert, of Merck & Company, Inc., donated the cortisone; Dr. R. Darlington, of the Department of Anatomy, University of Birmingham, made the statistical analyses of our data; Miss R. H. Lawrence gave technical assistance, and Dr. M. Beznak performed hypophysectomies.

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EXPERIMENTAL INTRAOCULAR INFECTION WITH MUMPS VIRUS

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EPIDEMIC parotitis is a virus infection which may manifest itself in multiple involvement of glandular and nerve tissue. The ocular manifestations of the disease may be divided into three categories: (1) involvement of glandular tissue (dacryoadenitis); (2) involvement of nerve tissue (optic neuritis, nystagmus, paralysis of extraocular muscles, paralysis of accommodation), and (3) involvement of ocular tissues proper (conjunctivitis, keratitis, scleritis, anterior uveitis, choroiditis). Clinical descriptions have been summarized by Bonnet [1] and Bolletieri.[2] A recent review of the literature has been compiled by North [3]; a number of published cases of mumps keratitis are summarized by Danielson and Long,[4] with more recent cases added by Lippmann,[5] Nectoux,[6] Roussel,[7] Fields,[8] and Michálek and Iserle.[9] No histological studies of human eyes affected by mumps are available.

Experimentally, mumps virus has been reported by Bolin and associates [10] to give a corneal reaction in the guinea pig on inoculation of the virus into the anterior chamber, associated with the formation of specific complement-fixing antibodies. The studies reported below, aside from confirming some of Bolin's observations, were concerned with the types of ocular lesions in the guinea pig in response to inoculation of living and attenuated mumps virus, clinical and histological observations, and the serological response of the animals to the various mumps antigens.

MATERIALS AND METHODS

Virus.—The Enders strain of mumps virus was received from Dr. W. Henle, of the Children's Hospital of Philadelphia, and kept in the bacteriological laboratory, Women's Medical College, by successive intra-allantoic passages in chick embryos. Eight-day-old chick embryos were inoculated with 0.2 ml. of virus dilution in sterile tryptose broth containing 500 units of penicillin and 0.1 mg. of streptomycin per milliliter. A needle was inserted to a ¼ in. (6 mm.) depth through a hole drilled in the shell over the location of the embryo approximately 3 mm. below the line delimiting the natural air space. Allantoic fluids were harvested after five days of incubation at 37 C. and tested for presence of virus by chick red blood cell agglutination. Fluids with titers of 1:256 or 1:512 were checked for sterility, pooled, and used for further passage or animal inoculation.

Virus Preparations.—Ultraviolet Irradiation: Virus preparations were inactivated by the method described by Henle and Henle,[11] as follows: Infected allantoic fluid was dialyzed in

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sterile Cellophane bags against 20+ vol. of buffered saline of pH 7.0 for 24 to 48 hours to remove urates. Dialyzed fluids were irradiated in open Petri dishes for 10 minutes at a distance of 3 in. (7.5 cm.) from a General Electric germicidal lamp with continuous mechanical shaking.

Heat-Killed Virus: Infected allantoic fluids were heated for 30 minutes at 60 C.

Antigens: Allantoic fluids and membranes were harvested after five days of incubation. The allantoic fluids provided the virus-bound, or V, antigen.[12] Twenty per cent suspensions in buffered saline were made of the allantoic sacs by emulsifying the tissue in a Waring Blendor for five minutes. After preliminary centrifugation at 2,000 rpm, the supernatant fluid was subjected to centrifugation in the angle centrifuge at high speed for one hour. The supernatant fluid obtained after this centrifugation was negative when tested for hemagglutinins and served as soluble (S) antigen.[12]

Preparations according to the methods described above from membranes of uninfected chick embryos of the same age served as controls for the antigen preparations. In addition to normal membrane suspension (NM), particulate components of normal chorioallantoic membranes (NOP) were used.[13] All antigens were stored at — 10 C.

Animal Inoculation.—Guinea pigs of 250 gm. or over were anesthetized with ether. A conjunctival forceps was used to immobilize the eye, and 0.03 ml. of fluid was injected into the anterior chamber with a 0.25 ml. tuberculin syringe fitted with a ½ in., 27-gauge needle. The needle was introduced through the sclera 1 mm. from the upper limbus. In corneal scarification experiments the cornea was scarified with a hypodermic needle, and a sterile swab dipped in allantoic fluid from infected eggs was rubbed over the scarified area. Other routes of inoculation included subconjunctival deposits and foot pad and intradermal injections. In all these experiments the same amount of virus was introduced, the volumes of diluent varying. In experiments with rabbits 0.05 ml. of fluid was introduced into the anterior chamber.

Guinea Pig Sera.—Blood was collected from guinea pigs before and at varying times after inoculation and permitted to clot. The serum was separated and inactivated at 56 C. for 30 minutes. The sera were stored in the frozen state at — 10 C. until used for tests.

Complement Fixation Tests.—The technique employed by Henle, Harris, and Henle[12] was used. Twofold dilutions of the sera were prepared, beginning with dilution 1:4. Of each dilution 0.1 ml. was transferred to each of five tubes, in order to obtain five series of increasing dilutions. Of these, the first received saline solution (serum control); the second, mumps allantoic fluid (V antigen); the third, supernatant fluid of mumps allantoic membrane suspensions (S antigen); the fourth, supernatant fluid of normal allantoic membranes (NM), and the fifth, normal organ particle suspension (NOP). The V and S antigens were used in optimal dilutions, i. e., 2 to 4 units of antigen, as determined by preliminary titration with a standard serum. NM and NOP antigens were titrated in a similar fashion against serum of a rabbit immunized with NOP antigen. Each antigen dilution was mixed with an equal volume of suitably diluted guinea pig complement, and 0.2 ml. of the mixture was added to the corresponding tubes. Desiccated complement was used and diluted so that 0.1 ml. contained 1.3 minimal hemolytic doses. After preliminary incubation of the antigen-serum-complement mixtures for 60 minutes at 37 C., 0.2 ml. of sensitized sheep cells (2.5% suspension) was added by automatic pipette. Two units of amboceptor, as determined by optimal titration technique, was employed. The test was read after further incubation for one hour. The last initial dilution of serum giving complete fixation of complement (no hemolysis) was considered to be the end-point. Positive sera of known titer and all other usual controls were included in each test.

Hemagglutination Test.—For this test 0.4 ml. of virus suspension was mixed with 0.2 ml. of a 1% suspension of washed fresh chicken red blood cells and the mixtures incubated at 4 C. until the erythrocytes had settled. The degree of agglutination was determined by the pattern formed by the cells at the bottom of the test tubes.[14]

Periodate Treatment: One milliliter of allantoic fluid negative for hemagglutination was mixed with 0.2 ml. of 0.1 M $NaIO_4$ and incubated for 30 minutes at room temperature. Thereafter the periodate was neutralized by 1 part of 40% dextrose.[15]

Eye Suspensions for Virus Recovery or Passage.—Guinea pigs were killed by a blow on the neck at a given time after inoculation and the eyes enucleated. The cornea, uvea, lens, and

retina were ground with sterile alundum * and emulsified in tryptose broth containing 500 units of penicillin and 0.1 mg. of streptomycin per milliliter to form a 10% suspension. These suspensions were centrifuged for five minutes in an International centrifuge at 2,000 rpm, and the supernatant fluids were stored in ampules in a solid-carbon-dioxide (dry-ice) chest until used.

Skin Test.—The skin test and control antigens were received from Dr. W. Henle. Their preparation has been described in detail.[16] The sides of the guinea pigs to be used were shaved, and 0.1 ml. amounts of each preparation were injected intradermally on opposite sides.

Histological Sections.—Small windows were cut into the posterior segments of the enucleated eyes, which were then placed in 4% neutralized formalin. Thereafter paraffin sections were prepared and stained by hematoxylin and eosin.

RESULTS

A total of 170 guinea pigs were inoculated with various preparations of mumps virus. Twenty-four hours after the injection of active mumps virus into the anterior chamber of the eye a number of changes were noted. A mild generalized conjunctivitis could be seen, with a distinct dilatation of perilimbic blood vessels, which formed a ring 1 mm. in width around the limbus and invaded the superficial layers of the cornea to a depth of about 1 mm. The cornea showed moderate haziness, usually through the entire cornea with the exception of a narrow clear zone around the limbus. The pupil was miotic. On slip-lamp examination the cornea appeared thickened. The epithelium and Bowman's membrane were normal. The corneal stroma revealed fine infiltrates, which were densest in the anterior third of the stroma; Descemet's membrane could not be examined in detail because of the interference by the corneal infiltrates, but it was found to be normal in the clear zone near the limbus. The state of the iris also could not be evaluated when viewed through the central portion of the cornea, but through the clear zone at the periphery the iris markings showed slight blurring and some cellular exudate. These changes are shown in Figure 1; for a comparison with a normal albino guinea pig eye, see Figure 2. Eyes enucleated 24 hours after inoculation and examined histologically showed normal epithelium and Bowman's membrane, edema of the corneal stroma, and many polymorphonuclear and small-round-cell infiltrates in the anterior third of the stroma. The posterior two-thirds usually showed mild edema, and Descemet's membrane and the endothelium appeared normal. The anterior chamber was usually free of exudate except in the angle, where some polymorphonuclear leucocytes were present. The ciliary body was filled with these cells. On occasion a fibrinous exudate thinly interspersed with polymorphonuclear leucocytes in the anterior and posterior chambers gave early evidence of iritis (Fig. 3).

Forty-eight hours after inoculation of active virus the conjunctival injection was increased, the concentric ring of perilimbic vessels remained unchanged, and the clouding of the cornea was moderately increased. At this time definite anterior uveitis was noted. The iris markings observed through the clear zone of the limbus were indistinct, and the pupil remained miotic. Histologically these eyes showed an infiltrate in the anterior third of the corneal stroma of a density equal to that found after 24 hours. An exudate, which consisted mainly of polymorphonuclear leucocytes and a small number of small round cells, was present in the anterior chamber. The iris and the ciliary body were densely infiltrated with polymorphonuclear leucocytes (Fig. 4).

* Electrically fused crystalline alumina.

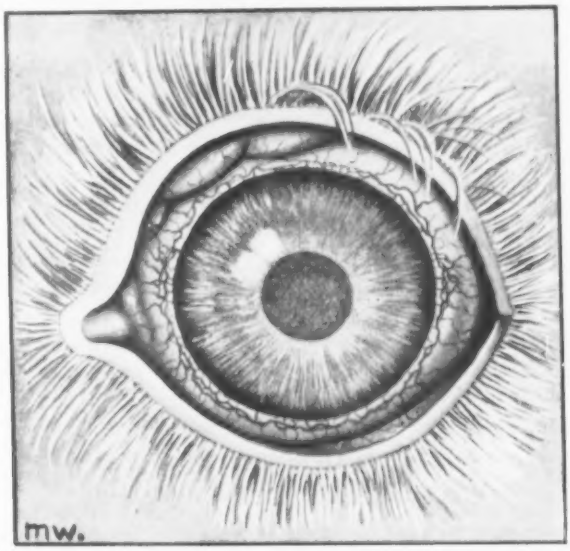

Fig. 1.—Albino guinea pig eye 24 hours after injection of living mumps virus into anterior chamber. Note chemosis of conjunctiva, dilatation of perilimbic ring of blood vessels, moderate haziness of cornea, fine clear zone at limbus, and slight degree of miosis. Drawing.

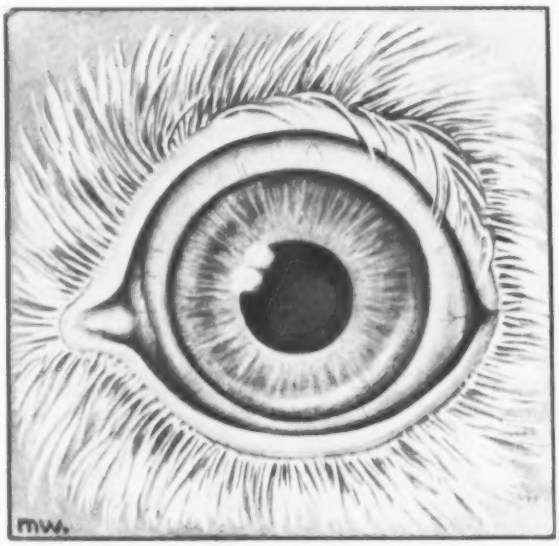

Fig. 2.—Normal albino guinea pig eye. Drawing.

Fig. 3.—Anterior segment of guinea pig eye 24 hours after inoculation with living mumps virus. Note edema of cornea, inflammatory cells in ciliary body, and fibrinous exudate with polymorphonuclear leucocytes in anterior and posterior chambers. Hematoxylin-eosin stain; × 27.

Fig. 4.—Anterior segment of guinea pig eye 48 hours after inoculation with living mumps virus. A marked exudative iridocyclitis is present. Hematoxylin-eosin stain; × 27.

Seventy-two hours after injection the conjunctivitis and the engorgement of the perilimbic vessels were diminished. The cornea began to clear, and the iris markings appeared distinct again: The pupil was wider than on the previous day, but still more miotic than normal.

On the fourth day the perilimbic vessels were only slightly dilated and the cornea showed a faint haze. With the slit lamp the cornea appeared normal in thickness. Some remaining infiltrates were observed in the anterior third of the stroma, and a few white specks were seen on Descemet's membrane.

On the fifth day after injection the eye appeared normal.

The clinical course varied from mild forms, manifested by corneal clouding, which appeared after 24 hours, reached the maximum after 48 hours, and completely disappeared after 96 hours, to severe forms, with different manifestations. Some of the severely affected animals showed mainly corneal involvement (Figs. 5 and 6), which consisted of a dense infiltration of the anterior third of the corneal stroma with polymorphonuclear leucocytes and small round cells and a moderate infiltration of the posterior two-thirds. In other animals the main change was an iridocyclitis with very little corneal involvement (Fig. 7); in yet others a deep interstitial keratitis was observed, with considerable ingrowth of vessels in the posterior third of the stroma and only mild involvement of the anterior uvea (Fig. 8). In some of the animals showing interstitial keratitis triangular limbus-based opacities developed and persisted throughout the period of observation of six weeks, while the remainder of the cornea became completely clear. The lesions of all other animals cleared completely after various intervals.

Complete recovery from a typical course, in which maximal corneal involvement was noted after 48 hours and all clinical signs had disappeared on the fourth day, is demonstrated in Figure 9. Another type of lesion, illustrating the persistence of vessels in the corneal stroma for many weeks after inoculation, is shown in Figure 10.

The cause of the variation in severity of the course may lie either in the variability of the virus inoculum used or in the variability of the individual responses of different animals. On some occasions a difference in the severity of lesions in the two eyes of the same animal injected with the same inoculum could be observed. The virus content of the allantoic fluid injected varied in different experiments from $10^{8.4}$ to $10^{9.0}$ $I.D._{50}$/ml. (50% infectivity end-point) as measured by infectivity in fertilized hen's eggs. The severity of the ocular lesions did not seem to be well correlated with differences in $I.D._{50}$. On the other hand, the injection of as small an amount as 0.03 ml. is subject to a relatively high experimental error, which is increased by a variable amount of back leakage when the needle is withdrawn.

The lesions described here could be produced only when the virus was introduced into the anterior chamber of the eye. No such changes were noted on injection of undiluted active virus subconjunctivally or by corneal scarification. In an attempt to find a minimal infective dose for anterior chamber inoculation, the virus inoculum was diluted 100 and 1,000 times (in this experiment an undiluted virus inoculum of $10^{8.2}$ $I.D._{50}$/ml. was employed) and injected into the anterior chamber. No pathological changes could be observed.

In two experiments in which the virus was exposed to heat prior to inoculation into the anterior chamber no clinical or histological changes in the eye were found.

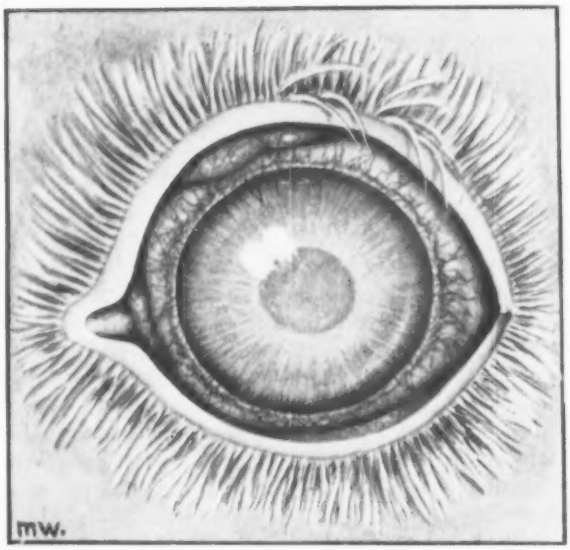

Fig. 5.—Albino guinea pig eye 48 hours after injection of living mumps virus into anterior chamber. The main inflammatory changes are confined to the cornea, which has become so cloudy that the outline of the pupil is barely visible. Drawing.

Fig. 6.—Anterior segment of guinea pig eye six days after inoculation of living mumps virus. The cornea is markedly thickened; the epithelium and Bowman's membrane are normal. The infiltration with polymorphonuclear leucocytes and small round cells is densest in the anterior third of the stroma. Note absence of the involvement of anterior uvea. Hematoxylin-eosin stain; × 27.

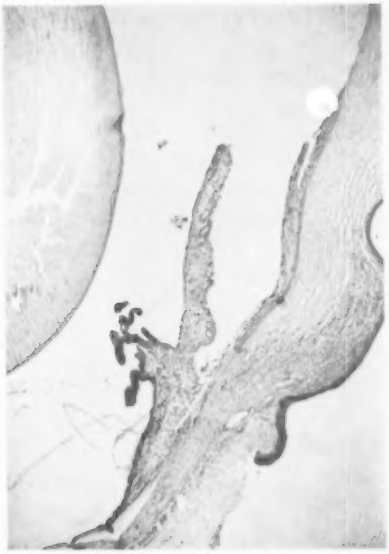

Fig. 7.—Anterior segment of guinea pig eye six days after inoculation of living mumps virus into the anterior chamber. The main pathological changes were confined to the iris and ciliary body, with barely any corneal involvement. Hematoxylin-eosin stain; ×27.

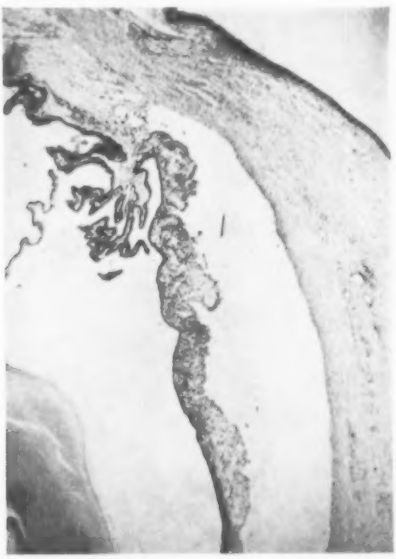

Fig. 8.—Anterior segment of guinea pig eye six days after inoculation of living mumps virus into anterior chamber. The main pathological changes were the ingrowth of large and small vessels into the posterior third of the corneal stroma.

Fig. 9.—Anterior segment of guinea pig eye six days after inoculation of living mumps virus. Four days prior to enucleation this eye had shown the usual parenchymatous keratitis and moderate uveitis. Note complete regression of all inflammatory changes and complete healing. Hematoxylin-eosin stain; × 27.

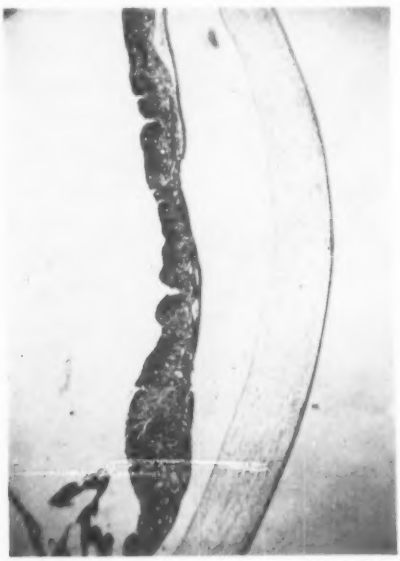

Fig. 10.—Guinea pig cornea and iris six weeks after inoculation of living mumps virus in anterior chamber. Note persistence of small capillaries throughout the cornea. Hematoxylin-eosin stain; × 27.

Three experiments with virus exposed to ultraviolet radiation were carried out. In the first two experiments a total of 10 guinea pigs were inoculated in the anterior chamber of each eye. None of the animals showed any clinical or histological changes. In a third experiment six guinea pigs were inoculated with the ultraviolet-irradiated virus in both eyes. Nine of these eyes developed a ciliary flush with a mild corneal haze 24 hours after injection, the response clearing by the third day. No changes were observed in the remaining three eyes. In all three experiments the virus had been inactivated completely by the exposure to ultraviolet light. No

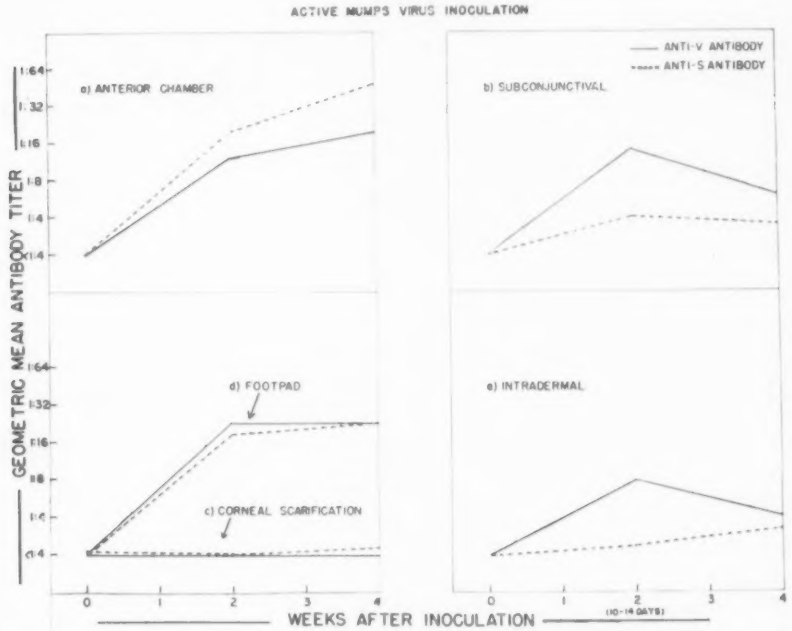

Fig. 11.—Antibody response against virus (V) and soluble (S) antigens of guinea pigs to active mumps virus injected into the anterior chamber of the eye, subconjunctivally, by corneal scarification, into the foot pad, and intradermally.

virus could be demonstrated on inoculation of the irradiated material into embryonated eggs and on subsequent passage. The $I.D._{50}$ of the virus before irradiation was $10^{5.4}$ and $10^{5.2}$/ml. in the first two experiments and $10^{7.24}$/ml. in the third.

Allantoic fluid harvested from uninoculated chick embryos and inoculated into the anterior chamber produced no lesions.

None of 28 rabbits inoculated in various experiments with active virus showed clinical or histological lesions. Neither did three rabbits inoculated with virus after it had been subjected to ultraviolet irradiation.

Serum samples taken at various intervals after anterior chamber inoculation with active mumps virus showed high titers of complement-fixing antibodies against virus (V) and soluble (S) antigen (Fig. 11*a*). Highest titers were obtained three weeks after inoculation (Fig. 12*a*). Comparative titers obtained by the inoculation

with active virus of groups of guinea pigs by subconjunctival deposit, corneal scarification, and foot pad and intradermal injection, are charted in Figure 11. It can be seen that on subconjunctival inoculation low antibody titers against soluble (S) antigens and somewhat higher antibody titers against virus (V) antigen are obtained, which reached their height two weeks after inoculation. A similar curve was obtained on intradermal inoculation. Antibody titers against S and V antigens after inoculation in the foot pad were higher, reaching their height after two weeks and maintaining it for four weeks. It can be seen from Figure 12 that geometric mean titers of antibodies against the two antigens were almost equal. A similar

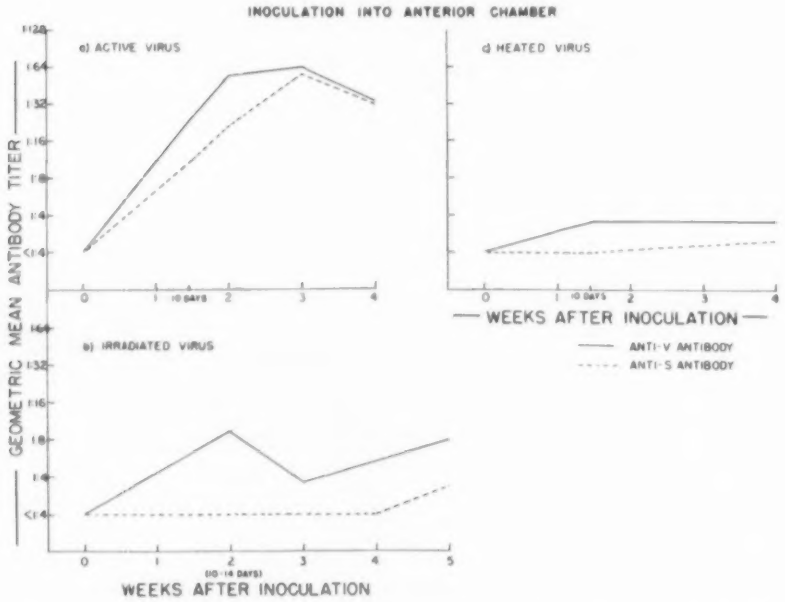

Fig. 12.—Antibody response against V and S antigens of guinea pigs to active mumps virus and to mumps virus inactivated by ultraviolet irradiation and heat injected into anterior chamber of the eye.

pattern can be seen on anterior chamber inoculation (Fig. 12*a*), showing curves obtained by the combination of the results of several experiments done at different times.

To see whether the consistently higher antibody titers, especially against the S antigen, obtained on anterior chamber inoculation were due to multiplication of the active virus in the eye, two inactivated preparations of mumps virus were used in several experiments. Guinea pigs were inoculated into the anterior chamber with mumps allantoic fluid which had been exposed to ultraviolet radiation, and another group of animals, with another portion of the same allantoic fluid inactivated by heating. The clinical appearance of these eyes has been described above. Production of antibodies expressed in geometric mean titers obtained by the combina-

tion of several experiments is summarized in Figure 12. Low antibody titers against V antigen were obtained with virus inactivated by ultraviolet irradiation, and even lower titers, with heat-inactivated virus. Antibody titers against S antigen were negligible in these animals. It is evident from these data that the highest and most persistent antibody levels against V and S antigens were obtained on injection of active virus into the anterior chamber of the eye. The minimal amount of mumps inoculum for antibody production has not been determined accurately. However, the following experiment was performed. Two groups of guinea pigs were inoculated in the anterior chamber, one with a 1:100 dilution and one with a 1:1,000 dilution of active virus. Neither group developed ocular lesions. No antibodies were demonstrable after a period of 10 days in either group; after 4 weeks all four animals in the 1:100 dilution group had developed antibodies against S antigen and two animals had developed antibodies against S and V antigens. In the 1:1,000 dilution group all three animals developed antibodies against S antigen and one animal antibodies against S and V antigens. As far as conclusions can be drawn from such a small group of animals, it seemed that the attainment of measurable titers required a longer time in the case of more dilute inocula, and in the case of V antigen as compared with S antigen.

None of the animals in any of the groups developed significant antibody levels against the normal tissue antigens employed in testing.

Observations on antibody production were made in a total of 10 rabbits inoculated with active mumps virus in the anterior chamber and of 3 rabbits inoculated with mumps virus after exposure to ultraviolet light. Several of the rabbits developed antibodies against normal tissue constituents, as indicated by a positive complement fixation test against NM and NOP antigens. After absorption of these antibodies with sheep red blood cells, no antibodies against mumps virus could be demonstrated.

Skin Tests.—A number of the guinea pigs injected with the various virus preparations and injected by various routes, and a group of albino guinea pigs which had never been exposed to the virus, were intradermally tested with mumps virus.[16] Two experiments were performed. In the first one the animals were skin-tested 1 month after the inoculation of virus and in the second after 11 weeks. All animals were bled prior to, and 1 week to 10 days after, the skin testing. Skin test read after 24 and 48 hours were uniformly negative in all groups. None of the normal guinea pigs developed antibodies after the skin test. As shown in Figure 13, a large number of animals with low antibody titers, or titers below the threshold of measurement, after exposure to active or inactive virus administered by various routes, developed substantially higher antibody titers against V and S antigens after the secondary antigenic stimulus of the skin test.

Virus Recovery.—Attempts were made to recover mumps virus from guinea pig eyes at various times after inoculation. Suspensions were made as described above and inoculated into eggs in dilutions ranging from 10^{-1} to 10^{-9}. Undiluted allantoic fluid harvest from each inoculated egg was tested for presence of virus by the hemagglutination test. Negative allantoic fluids were retested after treatment with sodium periodate to remove nonspecific inhibitors.[15] The 50% infectivity end-point ($I.D._{50}$) was calculated from these data.

In a preliminary experiment 10 guinea pigs were inoculated in the anterior chamber of both eyes with living, undiluted mumps virus. In the case of five guinea pigs the eyes were enucleated 48 hours after inoculation, and in the remaining five animals this interval was 5 days. Virus was recovered from all eggs inoculated with individual eye suspensions made 48 hours after infection, while only two of the eye suspensions made 5 days after infection showed evidence of presence of virus, and these only in low dilutions.

The results of a larger experiment are summarized in Figure 14. Seventeen guinea pigs were inoculated with virus in both eyes. The eyes of groups of three guinea pigs each were enucleated immediately, 24 hours, 48 hours, and 72 hours

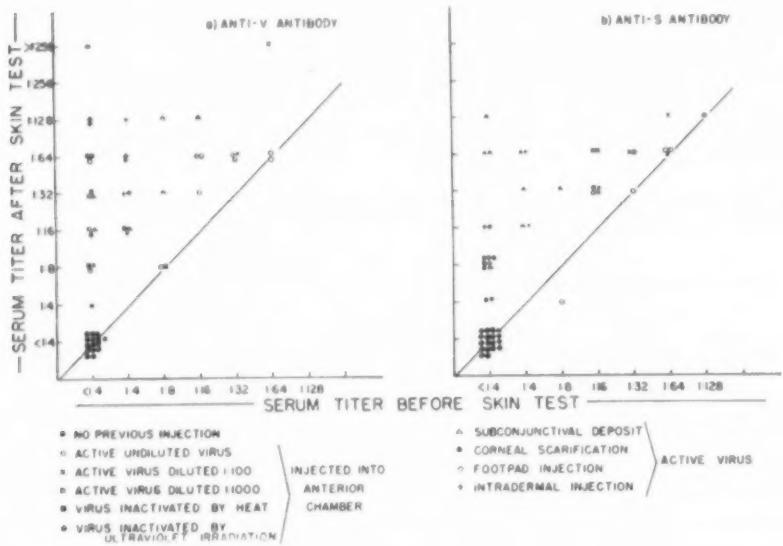
a) ANTI-V ANTIBODY
b) ANTI-S ANTIBODY
SERUM TITER AFTER SKIN TEST
SERUM TITER BEFORE SKIN TEST
<14 14 18 116 132 164 1128
• NO PREVIOUS INJECTION
○ ACTIVE UNDILUTED VIRUS
× ACTIVE VIRUS DILUTED 1100
⊕ ACTIVE VIRUS DILUTED 11000
■ VIRUS INACTIVATED BY HEAT
● VIRUS INACTIVATED BY ULTRAVIOLET IRRADIATION
INJECTED INTO ANTERIOR CHAMBER
△ SUBCONJUNCTIVAL DEPOSIT
▲ CORNEAL SCARIFICATION
◇ FOOTPAD INJECTION
◆ INTRADERMAL INJECTION
ACTIVE VIRUS

Fig. 13.—Comparison of antibody titers against V and S antigens before and after inoculation of mumps skin test material into guinea pigs which were previously untreated or had previously received injections of active or inactive mumps virus into the anterior chamber of the eye or of active mumps virus administered subconjunctivally, intradermally, subcutaneously, or by corneal scarification.

after injection. The eyes of a group of five guinea pigs were enucleated after 96 hours. Eyes in each group were pooled and suspensions made. Each suspension was injected in dilutions ranging from undiluted to 10^{-9} into groups of seven eggs per dilution. It can be seen from Figure 14 that the virus content of the eyes dropped with the lapse of time after inoculation.

In the three virus-recovery experiments performed, the $I.D._{50}$/ml. of the original allantoic fluid was $10^{9.41}$, $10^{9.14}$, and $10^{8.82}$, respectively.

No evidence of multiplication of virus in the eyes could be found. Complement-fixing and hemagglutinating antigen could not be demonstrated in any of the suspensions tested.

Eye-to-Eye Passage.—Attempts were made to pass mumps virus from infected guinea pig eyes to eyes of normal guinea pigs. Guinea pig eyes inoculated with mumps allantoic fluid in the anterior chamber and showing the usual pathology were enucleated. Suspensions of these eyes were inoculated into four guinea pigs, two of which had been bled prior to inoculation, to be tested for production of antibodies later. The eyes of the other two guinea pigs were enucleated after 48 hours, and four guinea pigs were inoculated with suspensions of these eyes, two to be used for further passage and two for antibody production. A total of four successive passages was performed. No lesions could be observed on clinical and histological

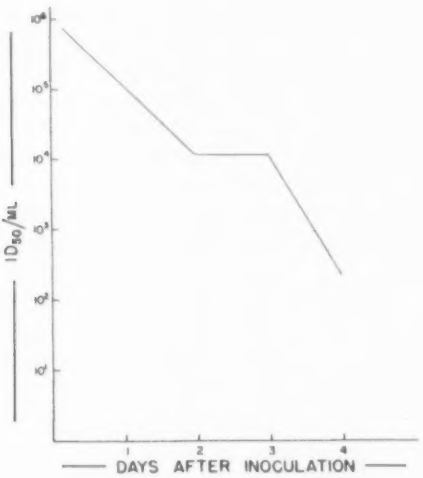

Fig. 14.—I.D.$_{50}$/ml. of mumps virus recovered from guinea pig eyes injected with active virus and enucleated immediately and one, two, three, and four days after inoculation.

examination in the inoculated eyes, nor could antibody production be demonstrated. In another experiment anterior chamber fluid was withdrawn from infected eyes and injected into the anterior chamber of two normal guinea pigs. No lesions were observed, and antibodies did not appear.

COMMENT

Ocular complications of epidemic parotitis in man are uncommon. Less than 25 cases of keratitis presumably due to mumps are reported in the literature. In most of these the diagnosis was made on the basis of the keratitis following the parotid swelling, which was believed to be due to the mumps virus on clinical evidence only. The usual clinical course of mumps keratitis described was rapid onset of photophobia, lacrimation, and decrease of vision following the parotic swelling in 3 to 12 days. The keratitis was usually unilateral. In the very few cases in which slit-lamp and corneal-microscope observations were recorded the parenchymatous keratitis is described as due to edema and the presence of white interlacing fibrillae.

The absence of vascularization has been noted. In most cases the anterior uvea was apparently not involved. The disease was self-limited, with complete healing in one to five weeks.

Considerable variations in the clinical manifestations were noted. Bolletieri [2] is the only one who describes a superficial punctuate type of keratitis; this was observed on his own eye by Bietti. In Michálek's case [9] the corneal epithelium stained with fluorescein. Most other descriptions seem to agree that the epithelium is usually unaffected. In the experiments on guinea pigs reported here no lesions on the epithelium or in Bowman's membrane were observed. The interlacing fibrillae described by Danielson and Long,[4] Lippmann,[5] and Fields [6] were not seen in the guinea pig. In our observations the characteristic changes were fine white dots in the anterior third of the thickened stroma. Similar dot-like opacities were described by Bonnet [1] in man. White streaks with dense centers in Descemet's membrane were observed by Nectoux.[6] Sagher[17] and Danielson and Long mention striate wrinkling of Descemet's membrane. In the guinea pig we were able to observe only a few white dots on the corneal endothelium and believed these to be keratic precipitates. Most authors describe the keratitis as involving the entire cornea, while Michálek,[9] Shoemaker,[18] Iribarren,[19] and Bonnet [1] speak of involvement of most of the stroma with the exception of a clear zone at the limbus. In this experimental series on the guinea pig the corneal stroma was uniformly involved but a clear zone remained near the limbus, through which the iris could be observed. Disciform and triangular limbus-based opacities in the corneal stroma have been described by Bonnet,[1] Lundsgaard,[20] and others; and these manifestations were also noticed among the variations in course encountered in our series of guinea pigs.

The interstitial keratitis with persistence of vessels in the posterior third of the stroma, as occasionally encountered in the guinea pig, has not been described in man.

The recovery from mumps keratitis in man is from one to five weeks. In the case of experimental infections in guinea pigs it was usually within four days, although in some animals it varied from five days to more than nine weeks, after which time the eyes were enucleated for histological examination.

The few cases of uveitis in man associated with mumps found in the literature vary in onset from 2 days prior to parotid swelling (Weskamp and Boccalandro [21]) to 20 days after its subsiding (Ortega [22]). The disease is usually unilateral. The usual onset of uveitis seems to be 11 to 12 days after the swelling of the parotid (Villard, Viallefont, and Teyssier [23]; Roussel [7]). The descriptions are those of anterior exudative iritis, which responded well to atropine and healed within about two weeks.

In our experiments on guinea pigs, involvement of the arterior uvea was present in almost all cases. It was observed both clinically and histologically as a mild cyclitis 24 hours after inoculation and had its peak on the second day. It rapidly subsided, and cleared within five days.

The ocular reactions reported above are much milder and much more akin to the clinical observations in man than the reactions described by Bolin and associates [10] on experimental inoculation of guinea pigs into the anterior chamber with the Enders strain of mumps virus. These authors describe a severe corneal reaction with pannus,

which was still present 18 days after inoculation. Virus of dilutions higher than to 10^{-2} gave transitory corneal reactions. The $I.D._{50}$/ml. of virus used by Bolin was of an average of $10^{9.3}$, which is considerably higher than the $I.D._{50}$ of the virus used in the experiments reported here. On only one occasion did our $I.D._{50}$/ml. reach $10^{9.05}$. The difference in infectivity of virus may account for the difference in severity of ocular lesions.

Ocular lesions were produced only by active living virus. Normal allantoic fluid and virus inactivated by heat or ultraviolet radiation did not cause ocular lesions. On the other hand, no multiplication of the virus in the inoculated eye could be shown with the methods used. Bolin and Leymaster's report [24] that the virus content of the inoculated eye drops rapidly has been confirmed here.

The studies reported here were confined to the anterior segment of the eye. Experiments to study the neurotoxicity of the virus on the retina and the optic nerve are in progress.

The virus could not be passed from the inoculated eye to a normal eye at the height of the ocular involvement, a fact which is consistent with the rapid disappearance of virus from the eye. The somewhat inconsistent appearance of virus on successive intraocular passage reported by Bolin and associates [10] has not been encountered in the experiments described here. The $I.D._{50}$/ml. of allantoic fluid of the original virus preparation used for our three passage experiments was $10^{8.2}$, $10^{8.4}$, and $10^{8.35}$, again lower than the average $I.D._{50}$/ml. employed by Bolin.

Guinea pigs having injections into the anterior chamber of living mumps virus responded with the development of high antibody titers against S and V antigens. Guinea pigs injected with virus inactivated by heat or ultraviolet radiation, or with active virus injected by other routes, produced lower antibody titers, especially against the S antigen. Development of S antibody has often been found to be directly related to virus infection.

The occurrence of negative mumps skin tests in guinea pigs which had previously been injected with active virus might be due to the fact that too little time was allowed to elapse between the original injection and the skin test. The rise in titer of complement-fixing antibodies after the skin test of guinea pigs with originally low or absent antibody titers after exposure to virus has an analogy in observations on man [25] in which the skin test seems to serve as a secondary antigenic stimulus in persons who have had subclinical infections without persisting antibodies.

SUMMARY

The Enders strain of mumps virus produces a keratitis with iridocyclitis in guinea pigs on inoculation into the anterior chamber. The typical clinical and histological lesions are described. Variations in the course of the infection are recorded.

Keratitis and iritis are produced only by active, living virus, not by virus inactivated by heat or ultraviolet irradiation.

The relationship of the experimental infection to the clinical mumps keratitis in man is discussed.

Guinea pigs receiving injections of mumps virus into the anterior chamber produce high antibody titers against the S and V antigens of mumps. Antibody titers

elicited by inoculation of inactivated mumps virus, or by inoculation of active mumps virus by subconjunctival deposit, corneal scarification, or intradermal or foot pad inoculation are consistently lower.

Guinea pigs tested with mumps virus skin test material 1 month to 11 weeks after the original contact with mumps virus gave a negative skin test. Guinea pigs with low or no antibody titer after the original contact with inactivated mumps virus or with active mumps virus injected by any route responded to the skin test with high antibody titers. The relationship of these findings to similar observations in man is discussed.

The Enders strain of mumps virus produced no lesions in rabbits on inoculation into the anterior chamber of the eye. No demonstrable complement-fixing antibodies against mumps antigens were produced in these animals.

Miss Evelyn R. Baker gave valuable assistance in this study.

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EXENTERATION OF THE ORBIT

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EXENTERATION of the orbit is a surgical procedure that has been carried out for many centuries. Since the original description of the operation by Bartisch,[1] a relatively small number of cases have been reported, and it was therefore thought worth while to review the cases of exenteration of the orbit performed at the Wilmer Ophthalmological Institute during the past 25 years.

REPORT OF CASES

During the 25-year period from 1927 to 1953, there have been 48 orbital exenterations performed at the Wilmer Ophthalmological Institute. Thirty-three patients were from the public wards and 15 were private.* Table 1 shows the race and sex of this group of patients. Thirty were males and 18 females. Four were Negroes, and 44 were white.

The ages of the patients at the time of exenteration are shown in Table 2. The youngest patient was 9 months old, and the oldest was 75. The pathologic diagnoses of these cases are shown in Table 3. Exenteration was done for malignant tumor in 44 cases and for inflammatory lesions in 4 cases. For purposes of discussion the series has been arbitrarily divided into four groups—the epidermoid carcinoma, the malignant melanoma, the sarcoma, and a miscellaneous group. These groups will be considered separately.

A. Epidermoid Carcinoma.—There were 14 cases in which exenteration was done for epidermoid carcinoma of the lids and face. In 12 cases the neoplasm was thought to arise from the lids; in 1 case, from the nose, and in 1 case, from the forehead. Some of the data on these cases are shown in Table 4. The ages ranged from 42 to 75 years at the time of exenteration. Ten patients were white men and 4 white women. The pathologic diagnosis was squamous cell carcinoma in 3 cases and basal cell carcinoma in 11 cases. In two cases the clinical histories have been lost and the final outcome is not known. Of the remaining 12 patients, 6 are known to have died of local recurrence, the interval between exenteration and death ranging from eight months to six years. Two patients were alive at the time of last examination, but with clinical evidence of recurrent tumor. The durations of follow-up on these two were 23 months and 3½ years. All attempts to obtain further information on these patients have been futile. Thus, in at least 8 of 12 cases exenteration of the

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* The following members of the Wilmer Institute staff permitted me to include their private cases in this series: Drs. A. C. Woods, J. S. Friedenwald, J. S. Guyton, F. B. Walsh, C. H. Bagley, C. E. Iliff, and W. C. Owens.

TABLE 1.—*Distribution According to Race and Sex of Forty-Eight Cases of Orbital Exenteration*

	Male	Female	Total
White	27	17	44
Negro	3	1	4
Total	30	18	48

TABLE 2.—*Distribution of Cases According to Age at Time of Exenteration*

Age, in Years	No. of Cases
Under 10	7
10 to 20	1
20 to 30	1
30 to 40	2
40 to 50	6
50 to 60	16
60 to 70	12
70 to 75	3
Total	48

TABLE 3.—*Pathologic Diagnosis in Forty-Eight Cases of Orbital Exenteration at the Wilmer Ophthalmological Institute*

Diagnosis		No. of Cases
Epidermoid carcinoma		14
Malignant melanoma		12
Sarcoma		9
Miscellaneous		13
Malignant tumors	9	
Inflammatory lesions	4	
Total		48

TABLE 4.—*Data on Fourteen Cases of Orbital Exenteration for Epidermoid Carcinoma of the Lids and Face*

Case	Age	Race	Sex	Diagnosis	Outcome	Duration of Follow-Up
E. B.	52	W	M	Basal cell	Dead, local recurrence	8 mo.
C. M.	51	W	M	Basal cell, face	Dead, local recurrence	3½ yr.
W. L.	42	W	M	Basal cell	Dead, local recurrence	4 yr. 3 mo.
A. M.	64	W	M	Basal cell	Dead, local recurrence	5½ yr.
L. P.	55	W	F	Basal cell	Dead, local recurrence	6 yr.
M. B.	75	W	F	Basal cell, nose	Dead, local recurrence	2 yr.
S. M.	60	W	M	Basal cell	Alive, recurrence	1 yr. 11 mo.
J. R.	46	W	M	Squamous cell	Alive, recurrence	3½ yr.
C. C.	65	W	F	Squamous cell	Alive, no recurrence	2 mo.
W. K.	74	W	M	Basal cell *	Alive, no recurrence	2½ yr.
A. E.	59	W	F	Basal cell *	Alive, no recurrence	5 yr.
H. H.	50	W	M	Basal cell	Dead, no recurrence	11½ yr.
R. L.	62	W	M	Basal cell	History lost	.....
T. R.	42	W	M	Squamous cell	History lost	.....

* Still under observation.

orbit was unsuccessful in completely removing all neoplasm. In the four remaining cases there has been no evidence of recurrent tumor. One patient survived 11½ years, only to die of an entirely different tumor, a carcinoma of the cecum. Three others were alive, with no clinical evidence of recurrence at the time of last examination. One of these disappeared from observation two months after exenteration, while the remaining two are still under observation two and a half and five years after exenteration.

In reviewing the individual case histories, one is struck by the tremendous time delay between onset of signs and symptoms of malignant lid lesions and adequate definitive treatment. Table 5 is an attempt to show this time lag. Eight of the 12

TABLE 5.—*Duration of Lid Lesion (by History) Prior to Orbital Exenteration in Twelve Cases of Epidermoid Carcinoma*

Duration, in Years	No. of Cases
3	2
4	1
5	1
6	1
7	1
8	3
9	1
15	1
Not known	1
Total	12

TABLE 6.—*Orbital Exenteration in Nine Cases of Malignant Melanoma of the Choroid*

Case	Age	Race	Sex	Outcome	Duration of Follow-Up
H. P.	51	W	F	Dead, myocardial infarction	18 days
M. S.	62	W	F	Dead, probable metastasis	8 mo.
J. W.	71	W	M	Dead, metastasis	2 yr.
H. C.	53	W	M	Dead, metastasis	2 yr.
G. G.*	48	W	M	Dead, metastasis	2 yr.
R. C.	57	W	M	Dead, "heart attack"	29 mo.
C. S.	57	W	M	Alive, "widespread metastasis"	7 mo.
K. W.	63	W	F	Alive, probable metastasis	3 yr.
H. Z.†	58	W	M	Alive, no recurrence	5¾ yr.

* Autopsy.
† Still under observation.

patients gave a history of a lid lesion for five or more years prior to exenteration. One cannot avoid the conclusion that orbital extension of carcinoma arising from the lids is the terrible price paid for ignorance or procrastination on the part either of the patient or of the responsible physician.

B. Malignant Melanoma.—There were nine cases in this series in which orbital exenteration was done for malignant melanoma of the choroid. Table 6 is a summary of these cases. The ages in this group ranged from 48 to 71 years. Three were white women, and six were white men. Six of these patients were dead within two and a half years of exenteration. One patient developed acute myocardial infarction on the 10th postoperative day and died 8 days later. No autopsy was obtained. Four patients died with clinical evidence of widespread metastasis. One patient died of a "heart

attack" 29 months after exenteration. There was no evidence of recurrence prior to death. One patient was alive seven months after exenteration, with evidence of widespread metastasis and a note, "prognosis hopeless." Another patient was last seen three years after exenteration, with no orbital recurrence but with a probable metastasis to the spinal cord. Attempts at further follow-up have been unsuccessful. Only one patient in this group is still alive and under observation, without evidence of recurrence, five and three-fourths years after exenteration.

A number of interesting points are revealed by study of the clinical histories in this group of cases. In four cases intraocular surgery had been performed prior to the diagnosis of melanoma of the choroid. In one case a corneoscleral trephination had been performed on an eye which had been blind for three years. Five weeks later the eye was enucleated, and a pathologic diagnosis of melanoma with extra-

TABLE 7.—*Final Observation After Orbital Exenteration in Three Cases of Malignant Melanoma of the Conjunctiva*

Case	Age	Race	Sex	Outcome	Duration of Follow-Up
I. S.*	54	W	M	Alive, no recurrence	4 yr. 8 mo.
G. T.*	60	W	M	Alive, no recurrence	9 yr. 4 mo.
A. T.*	60	W	M	Alive, no recurrence	14 yr. 8 mo.

* Still under observation.

TABLE 8.—*Orbital Exenteration in Nine Cases of Sarcoma*

Case	Age	Race	Sex	Diagnosis	Outcome	Duration of Follow-Up
J. S.	9 mo.	W	M	Rhabdomyosarcoma	Dead, no recurrence	4 wk.
G. F.*	3½	N	M	Rhabdomyosarcoma	Dead, metastasis	6½ mo.
S. G.	3	W	F	Sarcoma	Dead, recurrence	11 mo.
B. Z.*	5	W	F	Sarcoma	Dead, metastasis	7 mo.
M. S.	7	W	F	Sarcoma	Dead, metastasis	8 mo.
W. C.†	3½	W	M	Sarcoma	Alive, no recurrence	2½ yr.
M. F.*	62	W	M	Angiosarcoma	Dead, metastasis	5 wk.
R. C.†	14	W	M	Angiosarcoma	Alive, recurrence	31 mo.
P. W.	58	W	F	Angiosarcoma	Alive, ? recurrence	4¼ yr.

* Autopsy.
† Still under observation.

bulbar extension was made. In a second case a posterior sclerotomy and combined extracapsular cataract extraction had been done on a blind, painful eye. Eleven days later enucleation was done because of persistent pain, and a diagnosis of malignant melanoma was made. Ten years later orbital recurrence was noted and exenteration carried out. In a third case a Walker diathermy operation for retinal detachment was done one and a half years before enucleation revealed a malignant melanoma of the choroid with extension through the sclera. It is quite probable that in this case the detachment operation may have contributed to the spread of the tumor into the orbit. In a fourth case an ignipuncture for retinal detachment was carried out five months before enucleation established the diagnosis of melanoma. It is interesting that in this case, although there was a tumor in the sclera and a nodule on the external surface near the disc, the patient got along for 15 years before an orbital recurrence necessitated exenteration.

In three of the patients in this series orbital exenteration was done for malignant melanoma of the conjunctiva (Table 7). All were white men, and all three patients are still under observation without evidence of recurrence. One patient has been followed 4 years 8 months; another, 9 years 4 months, and a third, 14 years 8 months. The last patient has survived longer than any other in this series.

C. Sarcoma.—There were nine cases in this series in which orbital exenteration was carried out because of sarcoma. These cases are shown in Table 8. The patho-

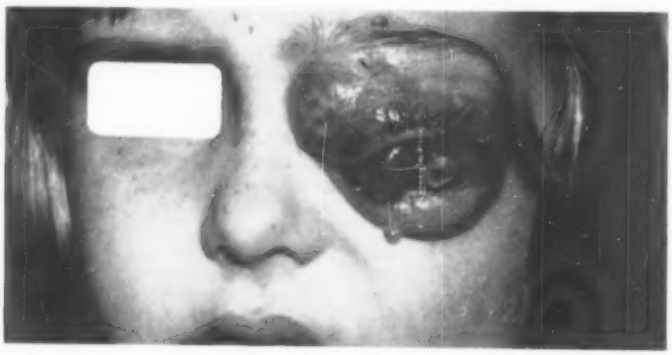

Figure 1

Figure 2

logic diagnosis was rhabdomyosarcoma in two cases, angiosarcoma in three cases, and undifferentiated sarcoma in four cases. The three patients with angiosarcoma were 14, 58, and 62 years of age, respectively. All the six remaining patients with sarcoma were under 8 years of age. The youngest patient in the entire series was a child of 9 months, in whom exenteration was done for rhabdomyosarcoma. Six of the patients were dead within 11 months of exenteration, and 3 were alive at last report. Two of the three patients still alive at last report had pathologic diagnoses of angiosarcoma, while one had a diagnosis of undifferentiated round cell sarcoma. One of these patients was alive without clinical evidence of recurrence two and a

half years after exenteration for round cell sarcoma and is still under observation. The second was living 31 months after exenteration for angiosarcoma and is still under observation. This patient had orbital recurrence following exenteration, but this recurrence responded well to implantation of radon seeds. The third patient was living but had clinical evidence of orbital recurrence four years three months after exenteration for angiosarcoma.

Although exenteration of the orbit is a mutilating procedure, in occasional cases it is justified for cosmetic purposes alone, as is well exemplified in one case (B. Z.) of this group. Figure 1 shows the patient before exenteration, and Figure 2, four weeks after exenteration. Although the patient died of generalized metastasis seven months after exenteration, there can be little doubt that the operation was a cosmetic success.

D. Miscellaneous.—There were 13 cases in this series with miscellaneous pathologic diagnoses. Nine were of various malignant tumors, and four were of inflammatory lesions. These cases are shown in Table 9.

TABLE 9.—*Orbital Exenteration in Thirteen Cases with Miscellaneous Diagnoses*

Case	Age	Race	Sex	Diagnosis	Outcome	Duration of Follow-Up
G. D.	2	W	M	Retinoblastoma, O. U.	Dead, metastases	1 yr.
J. C.	57	N	M	Mixed tumor, lacrimal gland	Dead, recurrence	2½ yr.
E. A.	39	N	F	Mixed tumor, lacrimal gland	Dead, recurrence	3¼ yr.
L. S.	54	W	M	Meningioma	Dead, recurrence	8 mo.
T. K.	27	W	F	Meningioma	Alive, no recurrence	2½ yr.
D. O'C.	62	W	M	Carcinoma of antrum	Dead, recurrence	6 mo.
A. W.*	60	W	F	Carcinoma, lacrimal sac	Alive, no recurrence	27 mo.
M. B.	63	W	F	Carcinoma of cornea	Alive, no recurrence	2 mo.
B. B.*	48	W	F	Carcinoma of conjunctiva	Alive, no recurrence	5¼ yr.
E. S.	57	W	F	Granuloma	Alive, no recurrence	7 yr.
H. E.*	43	W	M	Granuloma	Alive, no recurrence	10½ yr.
J. M.	51	N	M	Granuloma	Alive, no recurrence	2 wk.
N. K.	..	W	F	Tuberculous periostitis	Alive	2 wk.

* Still under observation.

Exenteration of the orbit was done in one case for retinoblastoma. A child of 2 years presented with the right eye completely destroyed and the orbit filled with tumor. The other eye was intact, but with tumor filling the vitreous cavity. The right orbit was exenterated and the child treated with x-rays. Death occurred one year later, of generalized metastasis. In two cases in this series exenteration was done for mixed tumor of the lacrimal gland. Both patients were Negroes, and both died of recurrence, two and one-half and three and one-fourth years after exenteration. There were two cases of meningioma in this group. One patient developed osteomyelitis and brain abscess and died eight months after exenteration. There was recurrent orbital tumor at the time of death. The second patient was alive, with no clinical recurrence, two and a half years after exenteration. Attempts at further follow-up have been unsuccessful. One patient in this series, with a carcinoma of the lacrimal sac, was alive, with no recurrence, 27 months after exenteration. One patient, with a squamous cell carcinoma thought to originate from the cornea, was alive, without clinical recurrence, two months after exenteration. One patient, with a basal cell carcinoma of the conjunctiva, was alive, without recurrence, five years three months after exenteration. One patient in this series had a carcinoma of the

antrum. Five years before exenteration a radical operation on the right antrum was done, with partial removal of tumor. The right orbit became involved with tumor, and exenteration of the orbit was done. The patient died with tumor recurrence six months after exenteration. In four cases orbital exenteration was done for what proved to be an inflammatory lesion. Three of these were cases of orbital granuloma or pseudotumor, and one was a case of tuberculous periostitis. In the first of the pseudotumor cases, the orbit was exenterated in 1929, and the histologic diagnosis was lymphosarcoma. The patient was alive, without recurrence, seven years after exenteration. The pathologic specimen was then reexamined, and on further study the diagnosis was changed to inflammatory pseudotumor. The second of these pseudotumor patients was alive, with no recurrence, 10½ years after exenteration. The third patient was alive two weeks after exenteration, but all attempts at further follow-up have been unsuccessful. It is of interest that these last two patients had had frontal craniotomy performed prior to exenteration in an attempt to establish a diagnosis. There was one patient in whom exenteration was done for tuberculous periostitis of the orbit. All attempts at follow-up on this patient have been unsuccessful.

E. Surgical Technique.—In this series, the surgical procedure consisted of removing the entire contents of the orbit, including the periosteum, with or without removing the lids. When the lids were not removed, they were used to cover the anterior portion of the orbit. This did not result in any cosmetic improvement, as compared with patients in whom the entire lids were sacrificed and the orbit was lined with a split-thickness skin graft. In no case was any attempt made to utilize the lids to retain an artificial eye.

For the last 10 years it has been routine to place immediately into the orbit a split-thickness skin graft obtained from the thigh. Prior to this time, the denuded orbit was allowed to granulate for some weeks before skin grafting was carried out. Immediate skin grafting has resulted in a much shorter healing time for the orbit and a much shorter period of hospitalization. Various types of prosthetic devices have been used to mask the deformity produced by the operation.

F. Complications.—There were two patients in this series in whom osteomyelitis of the orbit developed after orbital exenteration. In the first patient (L. S.) exenteration was done for meningioma of the orbit. No skin grafting was done. There was persistent discharge from the orbit postoperatively. Seven months after exenteration the patient noted severe headache and suffered one convulsion, with transient unconsciousness. Examination showed papilledema and pus draining from the orbit. Craniotomy was done, and a large frontal lobe abscess, secondary to osteomyelitis of the roof of the orbit, was drained. The patient did poorly and died three weeks after the craniotomy.

The second patient had orbital exenteration for basal cell carcinoma of the lid. A Thiersch graft to the orbit was placed six weeks after exenteration. The zygomatic bone remained exposed and became necrotic. Four months after exenteration the patient was readmitted, and a second Thiersch graft, with removal of necrotic and infected zygomatic bone, was made. Fifteen months after exenteration there was osteomyelitis of the roof of the orbit, and it was necessary to remove a large sequestrum from the orbit. The patient was alive, with probable recurrence of tumor, 23 months after exenteration. Attempts at further follow-up have been unsuccessful.

There was one patient (R. C.) in whom too thick a graft was obtained from the thigh. A Padgett dermatome was used to obtain the graft. The graft in the orbit sloughed completely, and regrafting was required. The original donor site likewise required skin grafting. This complication emphasizes the importance of obtaining a thin split-thickness graft.

There were a number of miscellaneous complications in this series of cases. One patient went into a marked depression and anxiety state in the immediate postoperative period, requiring psychiatric care. Two patients developed postoperative orbital infection with Pseudomonas aeruginosa. These infections ultimately responded to therapy, without serious consequence. Another patient developed infection of the skin graft, necessitating readmission to the hospital for further skin grafting. One patient had severe trigeminal pain postoperatively and ultimately required intracranial section of the trigeminal nerve.

There were four patients in this series in whom careful pathologic examination revealed no evidence of tumor in the tissues removed at the time of exenteration, although two of these later died of generalized metastasis. The first of these four patients (C. T.) had an enucleation for a malignant melanoma of the conjunctiva. One year later, a 5 mm. brown area was noted in the conjunctiva of the socket and exenteration was done. No tumor cells were found. The second patient (K. S.) was seen with a pigmented mass in the conjunctiva of the upper cul-de-sac. This was excised and found to be a malignant melanoma. Two months later the orbit was exenterated. There were scattered melanin-containing cells in the region of the previous mass, but no definite tumor cells. The third patient (M. S.) had enucleation of a blind, painful eye. The pathologic diagnosis was malignant melanoma of the choroid, with extrabulbar extension. The patient was referred here for exenteration five weeks later, but no tumor was found histologically. The patient died of metastasis nine months later. A fourth patient (S. G.) had a craniotomy, with removal of the roof of the orbit and removal of round cell sarcoma from the orbit. The neurosurgeons believed some tumor remained in the orbit, and a subsequent exenteration was therefore performed. However, histologic examination of the orbital contents revealed no tumor cells, although the patient eventually died with orbital recurrence.

G. Exenteration After Craniotomy.—There were three patients in this series in whom craniotomy, with removal of the roof of the orbit, had been done prior to exenteration. One (J. M.) had a craniotomy 16 months before exenteration. There were no complications at the time of exenteration. The pathologic diagnosis was orbital pseudotumor. Duration of follow-up in this case has been only 14 days. A second patient (H. E.) had three craniotomies prior to exenteration—five and a half years, three and a half years, and two years, before exenteration. The roof of the orbit was removed during the third craniotomy. There were no complications at the time of exenteration and none during the follow-up period, of 10½ years. The pathologic diagnosis was orbital pseudotumor.

The third patient (S. G.) had a craniotomy, with removal of the orbital roof and removal of orbital tumor, three months before exenteration. The pathologic diagnosis was sarcoma. At the time of craniotomy it was thought that tumor tissue remained in the orbit, and subsequently exenteration was carried out and a Thiersch graft placed in the orbit. Healing was uneventful until the 11th postoperative day, when there was herniation of the frontal lobe into the orbit. Twenty days after exenteration, a second craniotomy, with insertion of a tantalum plate in the roof of

Figure 3

Figure 4

the orbit, was carried out. Seven further operations were necessary to cover the roof of the orbit with skin. The patient died 11 months after exenteration with orbital recurrence of tumor.

These cases suggest that exenteration of the orbit may be safely carried out after the orbital roof has been removed only if sufficient time is allowed for bone regeneration to take place. If exenteration is contemplated shortly after removal of the roof of the orbit, the neurosurgeons should be requested to close the roof of the orbit with tantalum at the time of craniotomy.

H. Orbitosinus Exenteration.—There were six cases in this series in which exenteration of the accessory nasal sinuses was done, as well as exenteration of the orbit. The data on these cases are shown in Table 10. In none of these cases was

TABLE 10.—*Final Outcome in Six Cases of Orbitosinus Exenteration*

Case	Age	Race	Sex	Diagnosis	Outcome	Duration of Follow-Up
M. F.	62	W	M	Angiosarcoma	Dead	5 wk.
D. O'C.	62	W	M	Carcinoma of antrum	Dead	6 mo.
J. C.	57	N	M	Mixed tumor lacrimal gland	Dead	2½ yr.
W. L.	42	W	M	Epithelioma of lid	Dead	4 yr. 3 mo.
A. M.	64	W	M	Epithelioma of lid	Dead	5½ yr.
M. B.	75	W	F	Epithelioma of nose	Dead	2 yr.

TABLE 11.—*Apparent Cures Following Orbital Exenteration for Malignant Tumors*

Case	Age	Race	Sex	Diagnosis	Duration of Follow-Up
I. S.*	54	W	M	Melanoma of conjunctiva	4 yr. 8 mo.
G. T.*	60	W	M	Melanoma of conjunctiva	9 yr. 4 mo.
A. T.*	60	W	M	Melanoma of conjunctiva	14 yr. 8 mo.
A. E.*	59	W	F	Carcinoma of lid	5 yr.
B. B.*	48	W	F	Carcinoma of conjunctiva	5¼ yr.
H. Z.*	58	W	M	Melanoma of chorold	5¾ yr.
H. H.†	50	W	M	Carcinoma of lid	11½ yr.

* Still under observation.
† Died of unrelated carcinoma.

surgery successful in completely removing all tumor. All six patients died of local recurrence, at intervals ranging from five weeks to five and a half years from time of exenteration. Figures 3 and 4 show the appearance of one of these patients, with mixed cell tumor of the lacrimal gland, before and after orbitosinus exenteration.

I. Final Outcome.—There were 42 cases in this series in which exenteration of the orbit was carried out for malignant tumor and in which data are available for studying the final outcome. The excluded cases are the four of inflammatory lesions and the two in which the clinical histories have been lost. Of these 42 cases, 7 have become lost from observation after a follow-up period of less than three years. Of these seven, four had evidence of recurrence, and three no evidence of recurrence, at the last examination. These seven cases are, therefore, excluded. Three cases are still under observation but have been followed for less than three years. None of these three show clinical evidence of recurrence.

There remain 32 cases. Of these 32 patients, 17, or over 50%, were dead within three years of exenteration—14 from recurrence and 3 from other causes. The

remaining 15 patients survived three years or more after exenteration, but 8 of these 15 had orbital recurrence. Of these eight patients with orbital recurrence, five died of orbital recurrence after surviving from three to six years, while the remaining three with orbital recurrence were lost from observation after being followed for three years or more.

Thus, there remain seven patients who were alive, with no clinical evidence of tumor recurrence, three years or more after exenteration. These seven cases represent apparent cures. They are shown in Table 11. To this group might some day be added the three cases, still under observation, without clinical evidence of recurrence, but so far followed less than three years.

COMMENT

Exenteration of the orbit is an operation that must be reserved for malignant tumors involving the orbit. This makes it imperative that a definitive histopathologic diagnosis be established before undertaking the operation. Moreover, except in very unusual circumstances, exenteration of the orbit should not be carried out if there is evidence of tumor metastasis beyond the orbital region. If the tumor is limited to the orbit and accessory nasal sinuses, orbitosinus exenteration or extirpation of the orbit should be carried out. Therefore, it is necessary when considering orbital exenteration to utilize all possible diagnostic steps in determining the presence or absence of tumor metastasis or extension. Only with the knowledge of the exact histologic diagnosis and anatomical localization of the neoplasm can one reach an intelligent decision on the merits of orbital exenteration.

Extension of tumor from the orbit into the bony walls of the orbit or into the accessory nasal sinuses may sometimes be demonstrated preoperatively by x-ray studies or by careful ENT examination. At other times, however, in spite of negative or equivocal preoperative x-rays and nasal examination, it becomes evident at the time of exenteration that the orbital walls are grossly involved with tumor tissue. This occurred in several of the cases in this series. It is necessary, therefore, that at the time of exenteration the surgeon be prepared to proceed with removal of any involved bony orbital wall or accessory nasal sinus.†

Once the decision to carry out orbital exenteration has been made, the main question confronting the surgeon is the question of whether to preserve the lids or not. There are various opinions on this question in the literature.‡ Various surgical procedures have been devised to allow the use of an artificial eye following exenteration. These techniques require the utilization of both lids and usually involve a varying number of surgical procedures over an extended period of time. The few reported cases are superb demonstrations of ingenious surgical technique, but not of outstanding cosmetic success. This is understandable when one realizes that all extraocular muscles and the levator of the lid are absent. In the majority of cases in this series it would have been inadvisable to leave one or both lids.

It is obvious that in cases of malignant tumor involving the lids, conjunctiva, or cornea the proximity of the tumor to the lids makes any attempts to preserve the lids ill-advised. In the sarcoma group, there are a number of reasons for not attempting to preserve the lids. Once exenteration for orbital sarcoma has been

† References 2 through 4.

‡ References 5 through 16.

decided upon, every possible attempt must be made to remove all tumor surgically. No surgeon can be certain that the lids do not contain tumor cells. The final outcome in the sarcoma group is extremely poor—in our series six of nine patients were dead within one year of exenteration. It does not seem fair to complicate the final months of life of this group, usually children, with surgical procedures designed to produce a better cosmetic result. Furthermore, most of these tumors are radiosensitive, and the absence of the lids makes postoperative radiation easier and more effective.

Of our cases of exenteration of the orbit for malignant melanoma of the choroid with orbital extension, only two out of nine patients were alive three years after exenteration. Cosmetic surgery seems unwarranted in a group with such a poor over-all prognosis. However, since these tumors are not radiosensitive, leaving the lids will in no way inconvenience postoperative therapy. These tumors rarely invade the lids anteriorly, and probably there is no greater risk involved in leaving the lids than in removing them.

In the meningioma group one finds probably the most favorable situation for saving the lids and attempting to introduce an artificial eye into the socket. These tumors are slow-growing, rarely involve the lids themselves, and occur in an age group in which cosmetic appearance is extremely important.

It should be apparent that the decision as to whether the lids should be saved or sacrificed must depend upon many factors, the most important of which is the exact nature of the malignant tumor as determined histologically. It is likewise apparent, if our series is at all representative, that in the majority of cases in which exenteration is indicated no attempt to save the lids should be made.

In a number of cases in this series, enucleation of the eye had been performed some time prior to exenteration. In these cases the operation was much simpler to perform technically. It seems reasonable, therefore, to enucleate the eye as the initial step in orbital exenteration. In this way, also, the subsequent use of the cornea of the enucleated eye for corneal transplant is facilitated, without detracting in any way from the histologic examination of the orbital contents.

Kirby's technique [17] of immediately placing a split-thickness skin graft onto the bare bone of the orbit is an extremely valuable contribution. It has been used almost routinely in this series since 1944 and has resulted in a much more rapid epithelization of the orbit, with consequent fewer orbital infections, shorter postoperative hospitalization, and much simpler postoperative care. Various instruments are available for obtaining split-thickness skin grafts, including various knives for freehand use, and several mechanical dermatomes.

SUMMARY

Forty-eight cases of exenteration of the orbit, including six cases of orbitosinus exenteration, are presented. Surgical technique, operative complications, and final outcome are discussed.

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CORRELATION OF OCULAR CHANGES IN ESSENTIAL HYPERTENSION WITH DIASTOLIC BLOOD PRESSURE

Preliminary Report

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BY PAYING proper attention to certain clearly defined changes in the retina, it is possible for the general practitioner, as well as the ophthalmologist, to make those observations which will permit him to estimate, within reasonable limits of accuracy, the expected level of a patient's diastolic blood pressure, commensurate with these changes.

It is well known that during the course of hypertension remissions in blood pressure figures occur. During the periods of exacerbation, on the other hand, there take place such profound, irreversible changes in the appearance of the retinal vessels, particularly the arterioles, that they remain as permanent signs, to be read by him who will. So true is this that, although intercurrent coronary thrombosis will markedly lower the sphygmomanometer readings, it will alter not at all the retinal vessel changes developed during the high diastolic levels that were reached previously. Once a persistently elevated diastolic pressure has existed, there will always remain a telltale picture in the vessels of the fundus.

It is common knowledge that "in general the retinal changes run parallel with the severity of the hypertension" [1] when changes in the vessels are present together with hemorrhagic infarcts, ischemic infarcts (exudates), and involvement of the margin of the optic nerve head (Chart 1).

However, it is not so well known that even very early in the course of essential hypertension there are to be seen equally significant signs, which are practically pathognomonic.

Over a period of 20 years the conviction has grown that the diastolic pressure is directly proportional to the number and the degree of severity of these retinal changes. Such a well-defined personal impression should be open to objective proof. Therefore a search for some numerical system of grading, weighing, and classifying the physical findings in the fundus was started about 10 years ago.

A patient's retinal vessels as seen today reveal the results of yesterday's hypertension and suggest the probabilities of tomorrow. Hence it is in our early diagnosis and in preventive medicine that the hopes for the patient suffering from essential hypertension must find the basis.

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Statistical calculations were performed by Dr. S. Feitelberg, Department of Physics of Mount Sinai Hospital.

Read before the Section on Ophthalmology at the 102nd Annual Meeting of the American Medical Association, New York, June 3, 1953.

A claim to any finality of conclusions should not be read into this preliminary communication. The only purpose, rather, is a plea that this proposed way of examining the retina should be used in studying hypertensive cases. Augmented by data accumulated by other observers, this method of approach, then, may help to clarify the problems of early diagnosis, as well as those of classification, through some simple system of weighted values. These values may permit their expression in a formula available to any physician for appraising the severity of the hypertensive state, particularly the earlier cases which comprise Grade 1.

This preliminary report owes so much to the numerous earlier students in this field (from Marcus Gunn's [2] first classical contribution through Keith, Wagener, and Barker [3]; Wagener, Clay, and Gipner,[4] and Friedenwald,[5] down to Wilson [6]) that no further attempt can be made to give credit where it is due.

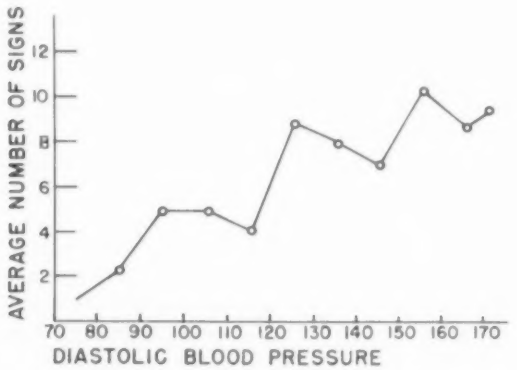

Chart 1.—The average number of signs per case is plotted against the actual diastolic blood pressures in this series of 100 cases, showing that there is a direct relation of the diastolic pressure to the number of signs and the degree of severity of the hypertension.

METHOD OF SELECTION OF CASES FOR THE STUDY

In the selection of cases for this pilot study, a concerted effort was made to keep from the examiner any information that might influence his opinion, supposedly based on solely objective ophthalmoscopic findings.

One hundred cases were studied, each one selected by the resident on the service, with the following seven safeguards:

1. Each session was held on a mixed group of patients with and without hypertension.
2. Each group contained different proportions of such patients.
3. The examiner had no inkling of the diagnosis or of the course of the patient's condition.
4. The findings were checked on an outline analysis sheet.
5. A note on the findings was dictated to the resident, who recorded it on the hospital chart.
6. I did not see the chart or talk to the patient until after this note on the chart had been dictated.
7. The outline analysis sheets were only completed some time after the fundus examinations were made, in order to add any other relevant clinical information, the age, and the blood pressure findings during the patient's stay in the hospital.

SELECTION OF EARLY SIGNIFICANT SIGNS AND TERMINOLOGY

It was decided that all the terms used in this study were to be simply descriptive, positive, and of precise meaning. Any finding open to doubt or question as to interpretation could not be used, such as color, relationship of artery to vein, corkscrew macular twigs, comparison with "normal" arterioles, or vasospasm. The term, once defined and described, should be acceptable to any other observer and easily recognized as such by him. Thus it became necessary to coin several new terms to describe irregular or focal narrowing in the arterioles.

A departure from the usual descriptive classification of the blood vessels was to divide the arterioles (A) and venules (V) according to their branching and to enumerate the segments between them: A1, A2, A3, A4, V1, V2, V3, V4. Accordingly, the anteriovenous crossing (AVX) received its numerical designation from that of the arteriole where the crossing occurred; for instance, A3 meant the third division of the arteriole; V2 meant the second division of the venule, and AVX3 meant the crossing of the vein over or under A3.

Uniform Narrowing (UN).—Both the normal arteriole and the normal vein are characterized by a gradual, continuous, uniform diminution in caliber from the optic nerve to the periphery. Between the divisions the segment of the vessel loses little in its diameter even if some tiny branches are given off. It is beyond the very point of branching that a distinct difference in diameter takes place. Even this recognition sometimes requires keen judgment, since by actual measurement the diameter of the parent stem has a relationship to the diameter of the dichotomous sibling branches of 10:8, or at most 10:7. To attempt to compare the width of an arteriole with the average normal was considered to be of even more indefinite value and unnecessary, since it involved the making of a decision which would vary with different observers. A further objection to considering the use of normal diameter was that the number of first branches is so variable. By elimination of the comparison of arterioles with accompanying venules, such as 5:4, 4:3, and 3:2, the problem was considered simplified, a branch being called narrowed only when the diminution in caliber was obvious.

In the data, the degree of narrowing was recorded by an exponent. $A2^4$ indicated a markedly narrowed second branch; $A4^0$ meant that the fourth branch was difficult to see or that it was obliterated. When the time came for total evaluation, it was decided that the narrowing of an arteriole was, in itself, more important than the degree to which it was narrowed. Therefore the degree of narrowing was dropped as an element of evaluation for the time being.

Irregular Narrowing (IN).—When a vessel narrows either gradually or abruptly and does not regain its expected caliber, it is termed a distal tapering (T). When a vessel is at first narrowed and then becomes wider for the rest of its course toward the periphery, it may be called a proximal tapering (PT). When a distal tapering of an arteriole (T) occurs in only one segment and then the vessel regains its former width, the sign is called an hourglass narrowing (HG). When several hourglass narrowings occur in one vessel, the condition is called beading (Bd).

Disproportionate Branching.—When one branch of a division is markedly narrowed but the other branch maintains its expected normal diminution in caliber, the sign is called a one-arm narrowed fork (Fl). When both branches are

pathologically narrowed and the branches do not regain their expected caliber, it is designated as a peripherally narrowed fork (F2). There are instances in which the stem is narrowed and the branching appears normal in caliber. This sign is labeled a proximally narrowed fork (PF).

Venule Narrowed (VN).—One of the most interesting observations made in this study was the participation of the veins in the phenomenon of narrowing. Some alteration in caliber of just one venule was noted in 20 cases and of more than one in 15 cases, making a total of 35 cases in which the venule was narrowed. In 11 of these cases this sign was seen in the absence of neuropathy or retinopathy.

All the signs described above, uniform narrowing (N), distal tapering (T), proximal tapering (PT), hourglass narrowing (HG), beading (Bd), one-arm narrowed fork (F1), distally tapered fork (F2), and proximally tapered fork (PF), may be present without retinopathy or neuropathy. Hence, these irreversible signs may be considered pathognomonic of established hypertensive disease in an ascending order of severity. In the 12 patients who were subjected to sympathectomy, so little improvement in arteriolar signs occurred that the appearance, to all practical purposes, remained unchanged, except in one in whom some improvement in vessel caliber may have taken place. The retinopathy and neuropathy in most cases were, on the contrary, remarkably improved, at times to the state of appearing normal.

Cotton-wool patches (ischemic infarcts) were recorded by the letter X, though the term exudate is no longer acceptable. Hemorrhagic infarcts were called simply hemorrhage (H), and edema residues were recorded as degeneration (D), in order to simplify tabulation and later evaluation.

Arteriovenous Crossings.—The arteriovenous crossings were recorded according to Duke-Elder's classification: concealment (C), lateral displacement (D), anterior displacement (D^A), posterior displacement (D^P), and banking (B).

Optic Disc.—The characteristics of the nerve head were classified as follows: clear (C); indistinct (I), if the margins were seen to be sharply outlined when the nerve head was transilluminated by focusing the image of the filament of the ophthalmoscope bulb (bare of condenser) on the central excavation; blurred (B), if the outlines of the nerve head could not be seen by streak ophthalmoscopy transilluminating the nerve head; edema (E), and elevation (L). Since C and I were within normal limits, they were included in the calculations but were omitted from the evaluation of the weighted significant signs.

The frequency distribution of the various signs was determined (in 67 of the patients) in order to gain some idea of their relative reliability in judging the contemplated weighted values. In the order of increasing frequency, and percentage of occurrence, the signs occurred as follows: star-shaped figure in the macula, 2%; silver-wire reflex, 3%; proximal tapering 3%; copper-wire reflex, 4.5%; one-armed fork, 6%; arterial reflex diminished, 7.5%; beading, 9%; hourglass narrowing, 13%; elevation of nerve head, 16%; narrowed fork, 16%; AVX anterior displacement, 16%; edema residue (D), 18%; AVX posterior displacement, 19%; proximal tapering, 22%; blurred margins of disc, 24%; edema of nerve, 25%; distal tapering, 31%; ischemic infarct (X), 34%; irregular narrowing, 36%; hemorrhage, 40%; arteriolar reflex increased, 46%; vein narrowed, 52%; AVX lateral displacement, 52%; AVX concealment, 57%; uniform narrowing of A1, 64%; banking, 64%; uniform narrowing of A4, 66%; A2N, 78%; and A3N, 82%.

Accordingly, the most frequent signs were the narrowing of the third, second, fourth, and first branches of the arterioles; then concealment and lateral displacement of the AVX; then VN and increased reflexes of the arterioles, and, finally, hemorrhage, exudate, etc., in diminishing order.

SUMMARY OF NONCONTROVERSIAL OPHTHALMOSCOPIC SIGNS IN ESSENTIAL HYPERTENSION

Studies of hypertensive changes in the fundi were made to determine the purely objective signs that could be recognized with ease by the general practitioner, as well as the ophthalmologist.

A. Arterioles
   1. Changes in reflexes
      (*a*) Diminution (—)
      (*b*) Increase (+)
   2. Tortuosity
      (*a*) Increased
      (*b*) Decreased (straightened vessels)
   3. Caliber—with reference to subdivisions, corresponding to the segments (A1, A2, A3, A4)
      (*a*) Uniform narrowing (UN)
      (*b*) Irregular narrowing (IN)
         (1) Tapering
            (*a*) Proximal (PT)
            (*b*) Distal (T)
            (*c*) Hourglass (HG)
            (*d*) Beading (Bd)
         (2) Disproportionate branching at the fork
            (*a*) One branch narrowed (F1)
            (*b*) Both branches suddenly narrowed (F2)
            (*c*) Proximal narrowing at with resumption of caliber beyond (PF)
         (3) Difficult visualization
         (4) Obliteration (ANO)
   4. Perivascular changes
   5. Arteriovenous crossings (AVX)
      AVX1, AVX2, AVX3, AVX4
      (a) Concealment (C)
      (*b*) Displacement
         (1) Lateral (D)
         (2) Anterior (D^A)
         (3) Posterior (D^P)
      (*c*) Banking (or compression) (Bg)

B. Venules
   V1, V2, V3, V4
   1. Uniform narrowing (UN)
   2. Irregular narrowing (IN)
   3. Tapering (T)
   4. Tapering at AVX (T)

C. Retinopathy
   1. Diffuse edema
   2. Ischemic infarct—exudate (X)
   3. Hemorrhage infarcts—hemorrhages (H)
   4. Edema residue—degeneration (D)

D. Optic nerve
   1. Indistinct margins (I)
   2. Blurred margins (B)
   3. Frank edema (E)
   4. Elevation (L)
   5. Detachment of retina

E. Choroidal changes
   1. With simple edema of retina
   2. With elevation of retina
   3. With detachment of retina

FORMULATION OF A TABLE OF UNIT VALUES PER SIGN

Any reference to blood pressure in this paper means diastolic blood pressure exclusively.

In order to attempt a statistical evaluation of the ophthalmoscopic pictures, it was necessary first to assign to each diagnostically significant finding (first column

of Table 2) a numerical value. This would create a table of weighted values which, though selected arbitrarily, would still be based on our clinical experiences. Several questions arose which had to be answered. It was obvious that edema of the nerve head is more important than, for instance, a single retinal hemorrhage. What was not so apparent was the relationship of A1N, A2N, to A1+2+3+4N. Is Pt weightier than F1 or PF? Is a narrowed V1 of any significance? And what about AVX? Do displacement and banking of AVX1 have any relationship at all to AVX2? The answers to these questions are, to be sure, not conclusive. But it did seem fairly obvious that one way of approach to the answers was to consider the increases in the measured diastolic pressures as though they were percentage deviations from the normal. Consequently, a base line has to be made from which one can figure out these percentage deviations. One can either assume an arbitrary normal diastolic pressure, say 85 or 90, or use the figures in Master's [7] tables of blood pressure levels in the general population adjusted for sex and age (Table 1).

TABLE 1.—*Normal Range and Limits of Hypertension* [7]

	Normal Range		Hypertension Lower Limit	
Diastolic Age	Male	Female	Male	Female
16	60-86	60-85	90	90
17	60-86	60-85	90	90
18	60-86	60-85	90	90
19	60-88	60-85	95	90
20-24	62-88	60-85	95	90
25-29	65-90	60-86	96	92
30-34	68-92	60-88	98	95
35-39	68-92	60-90	100	98
40-44	70-94	65-92	100	100
45-49	70-96	65-96	104	105
50-54	70-98	70-100	106	108
55-59	70-98	70-100	108	108
60-64	70-100	70-100	110	110

For each of our patients, the lower limits of the hypertensive diastolic blood pressure figures (adjusted for age and sex) in this Table were used as the base line of the diastolic pressure.

To illustrate this point, let us take Case 27, that of a woman aged 38, with an actual diastolic pressure of 145 mm. According to Master's table, the lower limit of hypertensive diastolic pressure for her age and sex is 100 mm. Hg. The increased deviation in her case was 45 mm. Hg, or + 45%. In Case 21, that of a man of 47, the diastolic pressure was 130 mm. Hg, i. e., 26 mm. Hg above the lower hypertensive level for his age, 104 mm. The percentage increase for this case was + 25%.

It was further assumed that the number indicating the percentage deviation of the blood pressure characteristic for each particular case could be used to apply equally to all the individual signs in that case.

The next step was to take a particular sign and list the percentages of blood pressure deviations. For example, there were 11 cases in which proximal tapering of an arteriole occurred. The diastolic pressures varied from 130 to 160 mm.; the percentage deviation adjusted for sex and age varied from —20%, at age 69, to + 55%, at age 39, totaling + 246%, which divided by 11 equaled + 22.4%. It

was assumed, then, that the average percentage deviation of the diastolic blood pressure for proximal tapering was about + 22%. For each of the significant signs the average percentage deviation was similarly found (second column of Table 2), and it was assumed to be characteristic for that particular sign. The third step was to arrange these averages in groups corresponding to nerve, retina, arterioles, and

TABLE 2.—Retinal Signs, Percentage Deviations, and Weighted Values

	Sign	Percentage Deviation	Weighting
Nerve	Blurring (B)	38	6
	Edema (E)	47	7
	Elevation (L)	48	8
Retina	Hemorrhage (H)	25	6
	Degeneration (D)	40	7
	Exudate (X)	43	5
Arteriole	A 4N	9	2
	A 1 + 3N	11	4
	A2 + 3 + 4N	15	6
	A1 + 2N	21	8
	A1 + 2 + 3N	25	10
	A1 + 2 + 3 + 4N	30	12
	A1 + 2 + 3 + (4) N(arrowed) with A4 obliterated	..	14
In	Tapering (T)	21	2
	PT: Prox. tapering	22	3
	HG: Hourglass N	37	5
	F: Narrowed fork	38	9
	F + PT	61	10
Vein	VN: Vein narrowed	11	3
	VN + neuroretinopathy	43	4
AVX	I B + D Banking and displacement	19	4
	II B + D	21	6
	III B + D	24	8
	IV B + D	28	10

NERVE	RETINA	ARTERIOLES UN		I R	VEINS	AVX
B-6	X-5	AI	1	DT-2	VN-3	AI-4
E-7	H-6	A4	2	PT-3		A2-6
L-8	D-7	AI+3	4	HG-5		A3-8
		A2+3+4	6	NF-7		A4-10
		AI+2	8			
		AI+2+3	10			
		AI+2+3+4	12			

UN VALUES DOUBLED IF E OR L PRESENT

Chart 2.—Condensed table of weighted values of the significant retinal signs.

AVX, and to factor them roughly in order to reduce them to round numbers. These round numbers (third column of Table 2) at first appeared to be random searchings for information, but after the calculations from the raw data were correlated, they actually showed that a relationship exists for the ophthalmoscopic findings, the patient's history and physical findings, and the clinical insight of the observer.

A very interesting situation developed in considering the data of the narrowed venous branches. Where changes in the nerve head were present (in 10 cases) the increased percentage deviation for narrowed vein was + 54.8%; in the 7 cases with retinopathy, the increased percentage deviation was + 23%, and when the narrowing was uncomplicated by either retinopathy or neuropathy, the increased percentage deviation for the VN was + 15% (18 cases). Altogether, there was a total of 35 cases in which one or more branches of the vein were narrowed. The average increased percentage deviation for all VN's was + 28.5%.

Finally, there was evolved a table of significant, pathognomonic retinal signs, their average percentage deviations from a hypertensive base line, and their arbitrarily assigned weighted point values (Table 2; Chart 2).

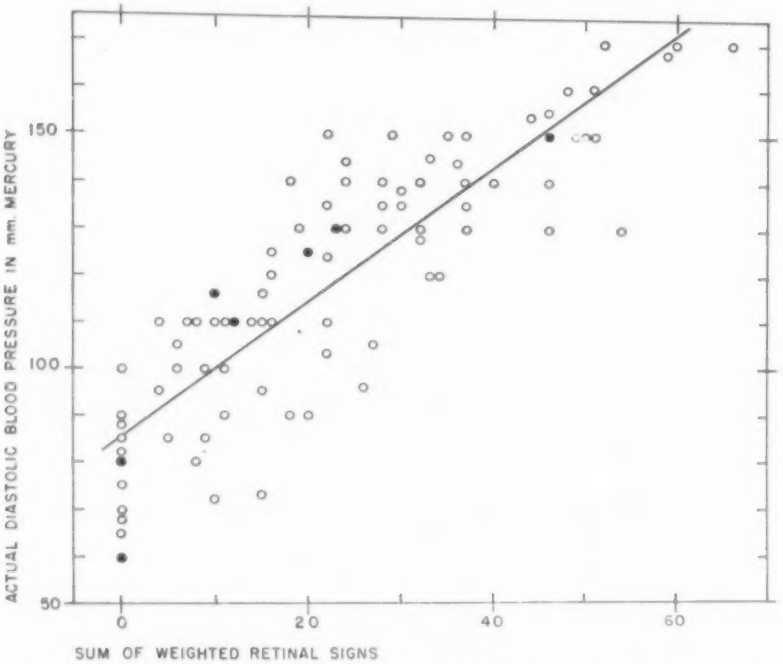

Chart 3.—Actual diastolic blood pressure of each patient plotted against the sum of weighted signs derived from pathognomonic ophthalmoscopic findings of each of the 99 patients. When a single point corresponds to two patients, it is indicated by a solid dot instead of a circle, except that the dot at 80 mm. pressure represents seven such patients.

STATISTICAL CALCULATIONS

1. For the purposes of correlating the ophthalmoscopic signs with the actual diastolic pressure by means of the point system developed in Table 2, a value varying from 1 to 14 was assigned to every diagnostically significant finding in the fundus in each case, counted but once regardless of how often the sign occurred in each case.

With these unit points as a basis, an ophthalmoscopic rating in points was calculated for every patient by adding together all the point values of each of the

signs found. Whenever either edema or elevation of the nerve was present, the unit values for the uniform narrowing of the arterioles had to be doubled in order to reflect the actual diastolic pressure.

The sum of all the point values may be called the weighted signs, which is represented by the symbol S in Equation 1 below. This rating system, although partially based on a clinical insight of the relative diagnostic importance of the various signs, is, nevertheless, quite arbitrary.

2. The relationship for every single patient of the actual diastolic pressure (P), in millimeters of mercury, as measured with the syphgmomanometer, to the sum of values, in points, for the ophthalmoscopic signs (S) is illustrated as rough data in Chart 2.

From this point, it should be understood that only the actual diastolic pressures and the sum of weighted signs of each individual case are being analyzed. No further reference to Master's hypertensive base line is considered in this statistical analysis of the data, since it was employed only to determine a probably valid percentage deviation of the diastolic pressure readings.

From Chart 3 the hypothesis could be formulated, therefore, that there is a correlation between the diastolic blood pressure and the ophthalmoscopic findings and that one can thus estimate the expected diastolic blood pressure on the basis of the fundus findings. Since the observed blood pressure (P) and the weighted signs (S) were obtained independently in 99 patients, and since both had definite numerical values, this hypothesis was tested by conventional statistical methods.

This test was made, and it was found that the coefficient of correlation between P and S was

$$r = 0.87 \text{ (which is significant)}$$

with a standard deviation of

$$\sigma_r = \pm 0.025$$

A correlation coefficient $r = 0$ means no correlation at all, and $r = 1$ means perfect correlation. This value of 0.87, together with a relatively small standard deviation of 0.025, is strong evidence for the validity of the hypothesis.

3. The statistical evaluation of the data in this study also gives the relationship between diastolic blood pressure and ophthalmoscopic signs according to the equation

$$P_e = 1.45\,S + 85 \qquad (1)$$

This equation (1) permits the calculation of an experimental estimation of a predictable level or value of diastolic blood pressure, P_e, for every individual patient by using the "weighted ophthalmoscopic signs" value (S) alone. The first number (1.45) in the right side of Equation 1 is a multiplication factor indicating the expected rise in diastolic blood pressure above an arbitrary normal for every unit of the point system; the second number (85) represents what appears to be "normal diastolic blood pressure."

It is possible now to calculate an estimated diastolic blood pressure P_e for every patient on the basis of the ophthalmoscopic fiindings and to see how well this estimate of pressure checks with the actually observed diastolic pressure.

If this calculation is done, it is found that the deviation (expressed as standard error of estimate, σ_e has the value

$$\sigma_e = 14 \text{ mm. Hg.}$$

This result means that the error of estimate will not exceed 14 mm. Hg in 68% of the patients, or that it is possible to predict diastolic blood pressure levels within ± 23 mm. Hg in 90% of the patients. Comparing this result, the estimated deviation of the blood pressures, as calculated from Equation 1, from the actual blood pressure, as measured directly, one sees that in the 99 patients the error was less than ± 23 mm. Hg in 89 cases, or in full agreement with the statistical prediction. This agreement indicates that the experimental values have a "normal" distribution in the statistical sense, adding further confidence to the result of the calculations.

COMMENT

When it is considered that in the statistical analysis there were 11 cases in which either the recorded actual diastolic pressure was affected by some intercurrent shock-like episode, such as myocardial infarct, coronary closure, brain hemorrhage, or metastasis, or there were higher diastolic readings recorded on the hospital chart than the one selected for the data, it can be realized that the deductions from the statistical evaluation of the raw data are very conservative.

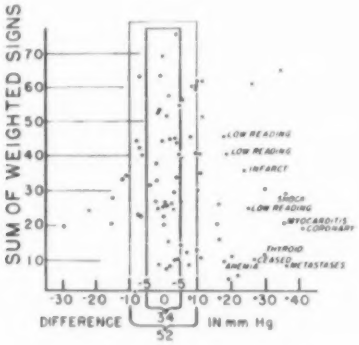

Chart 4.—The differences between the estimated diastolic pressure and the actual diastolic pressure of each case derived from equation $P_o = 1.45\,S + 85$, are plotted against the sum of weighted signs for each case. A total of 83 cases is thus shown. For 11 of these the reason for their being omitted from the calculation of percentages which reflect the reliability of the estimates is indicated by a comment.

In 47% cases the difference between the estimated and the actual diastolic pressures was within 5 mm. Hg; in 72% of cases, within 10 mm. Hg, if there was no failure in the blood pressure mechanism.

Chart 4 shows the differences found between the actual diastolic pressures and the estimated diastolic pressures commensurate with the fundus picture. Of a total of 83 hypertensive patients, the diastolic pressures were estimated within 5 mm. Hg of the actual pressure in 34, or in 41%. In 52 of 83, or in 62%, the estimates were within 10 mm. Hg. In eight cases there were myocardial or other general conditions which interfered with the maintenance of the blood pressure mechanism. There were three cases in which the blood pressure readings recorded on the hospital charts were higher than the readings used in the raw data. If these 11 cases are omitted (from the zone of greater error), as they should be, there is left a total of 72 cases. Of these, in 34, or 47%, the pressures were estimated within 5 mm. of the actual pressure. In 52 cases, or in 72%, the estimated pressure was within 10 mm. Hg of the actual.

There is nothing inconsistent in the concept of "estimated diastolic pressure" if the actual sphygmomanometer reading does not agree with the estimate, because the term has implicit in its meaning that there have been periods in the past when the diastolic pressure was elevated for a considerable time. If the estimate is higher than the actual diastolic pressure, it means either that the patient is in a state of remission or that some clinical condition, such as shock, coronary closure, or myocardial disease, has caused the pressure to drop. On the other hand, if the estimated diastolic pressure is lower than the actual, the assumption may be made that the blood pressure increase has psychogenic implications.

This report deals only with the raw data and leaves for the future (1) experimentation with weighted values other than those used in this report, (2) the question of arteriosclerosis, (3) the role of age and sex as factors in the estimation of the diastolic level, (4) the probability of enlarging the area and depth of Grade 1 hypertension, and (5) the possibility of developing a simple classification of hypertension based upon clinically estimated levels of diastolic blood pressure dependent upon a numerical system of weighted retinal values.

It is important to make sure that the values in Table 2 be considered as only the one experimental set of values that was used in the calculations by which this particular sampling of cases was analyzed. If these values were to apply to another group of cases, it would be merely coincidental. The possibility of these values being the final answer is necessarily a desired hope. Only evaluation of a number of other samplings could provide sufficient data on the general population for a final answer. The point to be made in this paper is that a system by which weighted values were assigned to retinal signs was successfully developed. Further investigation along this course might be made by other workers in this field for criticism and confirmation.

SUMMARY AND CONCLUSIONS

Ophthalmoscopic examination of the retina offers the general practitioner, as well as the ophthalmologist, a means of reading the full effects of past damage that attacks of essential hypertension leave, as a permanent recording, on the vascular system of the eye, in the very early stages of essential hypertension, as well as in later ones.

The recognition is facilitated by paying attention to several characteristic signs, for which new terms, such as tapering and tapered fork, are defined, especially since they occur mainly at the posterior pole of the eye.

The retinal vein participates, to a slighter degree than do the arterioles, in the phenomenon of vessel narrowing.

A systematic method of accumulating unbiased data is suggested for investigative purposes.

Data on 100 cases are analyzed by weighted signs based on increased percentage deviations from a base line of diastolic pressure.

The changes in the fundus are directly proportional to the previously established elevated levels of diastolic blood pressure.

The coefficient of correlation of the raw data in this series of cases is $r = 0.87$, with a standard deviation of ± 0.025.

It is possible to assign certain numerical values to each sign so that previously established blood pressure levels can be estimated in the individual patient within broad limits. In 47% of the hypertensive cases the diastolic pressures were estimated within 5 mm. Hg and in 72% within 10 mm. Hg.

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CAPILLARY TUBE METHOD FOR ANTIBODY DETERMINATION

Preliminary Studies in Aqueous of Rabbits Sensitized with Various Antigens

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THE SMALL amount of aqueous humor which is available for titration of antibodies is probably the chief factor that precludes the study of the ocular immunologic manifestations in sensitized animals. This investigation was an attempt, therefore, to apply an immunologic technique whereby the aqueous humor of one eye would be sufficient for antibody titration. Since the adaptability of the capillary tube method to immunologic studies has been demonstrated by Chown [1] for detecting the presence of Rh antibodies and by King [2] for conducting the milk test for brucellosis, this method was employed for determination of antibodies in the aqueous humor.

METHODS AND MATERIALS

Albino rabbits of varying weights and of both sexes were used throughout the study. Four animals were sensitized to bovine albumin * by three intravenous and by three intramuscular injections of 0.2 ml. of the antigen, at four-day intervals. Four other animals were sensitized in the same manner with 0.25 ml. of heat-killed Micrococcus pyogenes var. aureus (100,000,000 per milliliter). The animals in each group were bled by cardiac puncture prior to sensitization and at four-day intervals thereafter. Paracenteses were performed during the same periods. The samples of aqueous humor and serum were stored at —20 C. until used for titrations. Four to seven days after the last inoculation two rabbits from each group were subjected to paracentesis at half-hour intervals.

Attempts to confer dermal sensitivity on normal rabbits with aqueous humor were made as follows: One-tenth millililter of primary aqueous and the same amount of secondary aqueous were injected intracutaneously into two sites on the back of rabbits which had previously been shaven. Twenty-four hours later 0.1 ml. of the homologous antigen was inoculated into the same sites. Antigen and aqueous humor controls were included. Skin reactions were read within 1 hour and at 24 and 48 hours.

The capillary tubes were made of soft glass, 0.8 by 90.0 mm. The antigen was drawn up to approximately 6.0 mm., and an equal amount of aqueous was allowed to flow into the same end. Caution was exercised to prevent the entry of air bubbles. The tubes were inverted and inserted at a 45-degree angle into Plasticine. The inversion permitted the union of the antigen and aqueous. Controls for antibody and antigen were included. All tubes were incubated at 37 C. for three or eight hours. The tests were read against a white background under a strong light with the aid of a magnifying glass.

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Dr. Matthew C. Dodd, Ph.D., Department of Bacteriology, Ohio State University, made helpful suggestions in this study.

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* Bovine albumin, 30% solution, was obtained from The Armour Laboratories. Each milliliter contained 0.3 gm. of albumin prepared from bovine plasma.

FINDINGS

The primary aqueous humor of rabbits did not contain antibodies as determined by this method. However, immune bodies were demonstrable in subsequent samples taken at half-hour intervals. Animals sensitized with the cellular antigen demonstrated agglutinins, as evidenced by agglutination, with deposition along the walls of the capillary tubes after incubation for eight hours at 37 C. Precipitins, on the other hand, were demonstrated in the aqueous humor of rabbits sensitized with the soluble antigen. After three hours at 37 C. a ring formed at the interface of the

TABLE 1.—*Demonstration of Antibodies in Selected Rabbits Sensitized with Albumin and Micrococcus, Respectively*

	Primary Aqueous	Secondary Aqueous	Tertiary Aqueous	Quaternary Aqueous	Antigen Control	Antibody Control
Rabbit XI (albumin-sensitized)						
Right eye	—	+	+	+	—	—
Left eye	—	+	+	+	—	—
Rabbit ZI (Micrococcus-sensitized)						
Right eye	—	+	+	+	—	—
Left eye	—	+	+	+	—	—

TABLE 2.—*Titration of Antibodies in Aqueous Humors of Select Rabbits Sensitized to Micrococcal Vaccine*

	Aqueous Dilutions						Antigen Control	Aqueous Control
	1:1	1:2	1:4	1:8	1:16	1:32		
Rabbit JI								
Primary aqueous	—	—	—	—	—	—	—	—
Secondary aqueous	+	+	+	—	—	—	—	+*
Tertiary aqueous	+	+	+	—	—	—	—	—
Quaternary aqueous	+	+	+	—	—	—	—	—
Rabbit JII								
Primary aqueous	—	—	—	—	—	—	—	—
Secondary aqueous	+	+	+	—	—	—	—	—
Tertiary aqueous	+	+	+	+	+	—	—	—
Quaternary aqueous	+	+	+	+	—	—	—	—
Quintan aqueous	+	+	+	—	—	—	—	—

* Positive aqueous control may be due to specific antibody combining with residual antigen intraocularly.

antigen and the aqueous humor. Similar results were obtained with the sera. Microscopic examination of the plasmoid aqueous humors stained by Wright's method did not reveal the presence of any leucocytes, and the plasmoid aqueous differed from the primary aqueous only by the presence of fibrinous material.

Table 2 shows the results of titration of antibodies in the aqueous humors of animals sensitized with the micrococcal vaccine. There was no appreciable difference in titers of the secondary, tertiary, and quaternary aqueous humors.

Attempts to confer dermal sensitivity with the primary and secondary aqueous humor revealed the absence of antibodies in the primary sample and the presence of the immune bodies in the secondary aqueous, as manifested by a severe erythema and induration at the inoculation site in 24 hours.

COMMENT

The capillary tube method as described here permits the use of small quantities of aqueous humor for quantitative titration of antibodies, as well as titration of a series of antigens against a sample of aqueous humor. Both precipitins and agglutinins may be demonstrated by this method.

The absence or low titers of antibodies in the primary aqueous as tested by classic immunologic procedures is not a new phenomenon. Forty years ago it was established that puncture of the anterior chamber, as well as naturally occurring ocular inflammatory processes, produced a plasmoid aqueous in which the protein content approximated more nearly that found in the serum. Likewise, no antibodies could be detected with the capillary tube method in the primary aqueous humors of animals which were actively sensitized. That specific antibodies were present in the secondary aqueous was confirmed by conferring dermal sensitivity on normal animals.

The insignificant rise in antibody titer in the tertiary and quaternary aqueous humors as compared with that in the secondary aqueous might be explained by the fact that after the blood-aqueous barriers are destroyed, the globulin diffusion in the anterior chamber during half-hour intervals is similar in character, both quantitatively and qualitatively.

At the present time we are attempting to apply this method of titration to the aqueous humor of patients suffering from nongranulomatous uveitis with a series of antigens which have been incriminated as possible etiologic agents. With this procedure one could attempt to correlate skin reactivities of such patients with the specificity of antibodies found in the aqueous humor.

SUMMARY

A method is described whereby small quantities of an aqueous humor sample may be titrated against a series of antigens. The presence of antibodies in the aqueous humor of animals sensitized with bovine albumin and micrococcal vaccine, respectively, were demonstrated by the capillary tube method and by conferring dermal sensitivity on normal rabbits with secondary aqueous humor. The practical application of such a diagnostic method in cases of nongranulomatous uveitis is presented.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

VISUAL LOSS FOLLOWING CARDIAC ARREST

PATIENTS with visual loss following cardiac arrest and the reactivation of the heart will probably be seen more frequently today than in the past, owing to the increasing number of recoveries.

Today patients who in the past would have died of cardiac arrest are living, owing to Beck's [1] work on electric stimulation of the fibrillating heart and the lesson we have learned, that of rapid opening the chest or abdominal cavity and manually massaging the heart.

Hanks and Papper,[2] in discussing the diagnosis of cardiac arrest, stated:

> The moment the pulse or blood pressure is not obtainable the surgeon should be notified. The surgeon then palpates or inspects a vessel in the operative field. . . . Auscultation . . . is usually a waste of valuable time. Even electrocardiographic observations may not offer conclusive proof of cessation of the heart beat. Negovski [3] has shown that the heart can produce electrical activity after it has stopped beating.

Weinberger, Gibbon, and Gibbon [4] have shown in cats that arrest of cerebral circulation for 3 minutes 10 seconds or less was tolerated without any obvious neurologic disturbances. When, however, 8 minutes 45 seconds or longer transpired in the interruption of cerebral circulation, life could not be restored for more than a few hours. The incidence of complete recovery following cardiac arrest or ventricular fibrillation occurring at operation is less than 10%, as found in the literature and confirmed by documentation.

Hanks and Papper reported on 23 cases of cardiac arrest, 1 of which is of interest to the ophthalmologist. The patient was a 26-year-old white man whose cardiac arrest was dependent upon a postoperative severe hemorrhage. The pupils did not react to light, and light perception was not apparent. By the 10th day peripheral vision was regained. By the 30th day good intellectual capacity was evident. By the 50th day vision was good enough that he could read headlines in the newspaper. He had a permanent residual partial visual defect. In this case one cannot determine what part of the visual loss was due to cardiac arrest following the hemorrhage and what part was due to the postoperative hemorrhage itself.

The case of a baby * that I saw Dec. 11, 1953, however, is definitely one of visual loss following cardiac arrest.

> On Dec. 8 the baby, an 8-month-old boy, was operated on for hernia and hydrocele under ether anesthesia. One hour after the anesthetic was started the heart ceased beating. An abdominal incision was made and the heart massaged. The entire time from the first notation of the absence of the heart beat and the resumption of the heart beat was between three and three and one-half minutes. My first examination was on Dec. 11. The child's pupils reacted to light, but there was no recognition of objects. Light perception, however, was present, as noted by

* This case was seen through the courtesy of Dr. Jacob Levine.

blinking when a light was thrown into the eye. A vacant stare replaced the usual appearance when vision is present. The fundi were normal except for retinal venous congestion. There was no evidence of retinal edema in spite of the history of anoxia.

The child was apathetic and on the fifth day developed a tremor of the upper extremities with ataxia. Neurological examination was otherwise negative. No abnormal reflexes were present.

On the ninth day vision returned and the tremor became less pronounced. The baby's regard was directed to objects presented, including the return of convergence on near objects, such as one would expect from a normal 8-month-old infant.[5] Thirteen days after operation, he seemed normal except for some irritability. Now, seven weeks after operation, no abnormalities can be noted.

Cardiac arrest occurs in 1 of 2,500 cases of anesthesia. It may follow many types of anesthesia—ether, cyclopropane, or thiopental (Pentothal).

The incidence of cardiac arrest is on the increase. At the College of Physicians and Surgeons and Presbyterian Hospital, in 1947, out of 9,904 operative cases there were 2 cases of arrest, with 1 complete recovery. In 1948, out of 12,157 cases, there were 6 cases of arrest, with 1 recovery. In 1949, of 13,654 cases there were 7 cases of arrest, with 2 recoveries, and in 1950, of 14,013 cases, 8 cases of arrest, with 6 complete recoveries, or a 75% incidence of recovery.

The last figure is encouraging from the standpoint of life, but ophthalmologists must bear this condition in mind and expect to see such cases.

It is well to remember that after asystole the cardiac muscle has increased irritability in the first four minutes, rising to its peak, but that after this the irritability decreases and at eight minutes is less than normal. Electrical stimulation, if it is used, should be done as soon as possible, preferably within three minutes.

Every anesthetist should see that his institution has a definite procedure for the treatment of cardiac arrest and that all surgeons have an intimate and thorough knowledge of this procedure. The group should include a time keeper.

From a preventive standpoint, it has been shown that in a percentage of cases cardiac arrest is due to too much anesthesia. This accident, of course, should never occur.

It would seem that edema of the cortex, rather than local retinal pathology, accounts for the visual loss.

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Annual Review

OPTICS AND VISUAL PHYSIOLOGY

A Review of the Literature for 1953

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RESEARCH and writing on optics and visual physiology are being done by artists, astronomers, educators, ophthalmologists, opticians, optometrists, orthopists, physicists, psychologists, physiologists, and interested amateurs. In such a broad field, only the highlights can be included here.

INSTRUMENTS

Methods of exact measurement of the thickness of the cornea and the depth of the anterior chamber were applied to ophthalmic practice, particularly in cases of uveitis, keratitis, glaucoma, and keratoplasty by de Leonibus,[1] Paycha,[2] and Lister and associates,[3] Jaeger,[4] and Stenström.[5] Instruments like the retinoscope, optometer, pupillometer, and keratometer might be improved by the use of infrared light, according to Knoll.[6] Methods of electronic flash retinal photography are described by Hansell and Beeson[7] and Ogle and Rucker.[8] New methods of ophthalmoscopy are described by Ridley,[9] Arkin,[10] and El Bayadi.[11]

MYOPIA

There has been no lack of theory and controversy about factors contributing to the increase of myopia during childhood. Holst[12] found that 94 of a group of blind Norwegians were highly myopic. Of the myopes, 37 were males and 57 females. He suggested that pathological myopia is hereditary and recessive in the male. Hirsch[13] collected a series of cases of myopia exceeding 6 D., in which 11 were males and 26 females. However, of a group having less than 6 D. of myopia, 1,082 were males and 929 were females.

While the idea that myopic eyes are long and hypermetropic eyes are short appears in textbooks for children all over the world, Hulsman,[14] an educator, states that the innervational theory for the etiology of ametropia must also be considered.

By x-ray stimulation of the dark-adapted retina according to the Rushton method, Sorsby * measured the axial and equatorial diameters of ametropic eyes. Statistical correlation with total refraction, and the curves of cornea and lens showed that about two-thirds of the amount of ametropia is due to a variation in axial length and one-third is due to variations in cornea and lens curves. More important, he emphasizes a point in conflict with the Steiger theory, which differentiates myopia of ordinary powers from emmetropia and hypermetropia. Steiger believed that ametropia between + 6 D. and — 6 D. is an accidental statistical com-

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* References 15 and 16.

bination of freely variable curvatures and axial lengths. Since in myopia the globe is longer than it is high or wide, and in emmetropia or hypermetropia the globe is spherical, ametropia is not a free statistical process. Myopia is a disease process dependent on hereditary and other factors.

By the same x-ray technique, Kanefujl[17] measured the axial length of 475 eyes for comparison with refractive power and cornea curves. She found a difference in the correlation coefficients for myopic eyes and those for emmetropic and hypermetropic eyes. The correlation between total refraction and axial length was —0.78 in myopia, but —0.56 in nonmyopia. The correlation of refractive power and cornea curve was —0.03 in myopia and —0.56 in nonmyopia. Her figures showed that three-fourths of the myopia was due to increased axial length, while only one-fourth was due to increase in cornea or lens curves. Only slightly more than half the hypermetropia was due to axial length. These data are also in conflict with the Steiger theory and distinguish myopia from other forms of ametropia.

Gleiss and Pau[18] attacked the difficult problem of retinoscopic refraction of premature infants for information about the development of ametropia. Tests of 23 premature infants with eyes treated with homatropine were repeated at two-week intervals until the age of 6 or 8 months. Twelve infants showed hypermetropia from +0.50 to +4.50 D., which gradually increased. Seven showed myopia of from —1.00 to —3.00 D., which changed to emmetropia or hypermetropia. Four remained myopic. A relation of myopia to prematurity and of hypermetropia to hypermaturity has been mentioned in the literature but calls for more confirmation.

Badtke † studied embryonic eye sections, looking for signs of weakness of the sclera which might lead to myopia. In some sections he found bulging temporal to the optic nerve but thought it a normal compensation for the normally rapid growth of that part of the retina at the time. One such specimen showed a fold in the retina from rapid growth. He emphasizes that the shape of the embryonic globe is determined by the retina until the time when intraocular pressure develops. He concludes that myopia is a hereditary defect in growth, not a congenital weakness of the posterior sclera. He adds that the onset of myopia at school age and the aggravation by eye movements in reading give evidence against the congenital theory.

Ametropia accompanies hereditary deafness, according to Stockwell.[21] Of a group of 960 deaf children, 45.5% needed glasses, as compared with a normal incidence of about 20%. Of the deaf children needing glasses, 18.4% were myopic, a figure which conforms to the normal incidence of myopia in young adults.

The Lindner theory that corneal inflammation weakens the sclera of the posterior pole is supported by Rumpelhardt.[22] Among 12,000 cases of myopia, more than 5,000 were found to have corneal scars from injury or inflammation of significant severity.

The sight-saving class for the treatment of pathological myopia in children all through school was advocated by Barfoed.[23] His statistics show that the increase in myopia became less rapid during attendance in special classes and that myopia in the same cases resumed a more rapid rate when the children were transferred to regular classes. He concludes that myopic children should do little near work regardless of age or school grade.

† References 19 and 20.

In most studies of the change in refraction, figures represent the averages for a group. Bücklers,[24] paper is of unusual importance because the increase in myopia of individual eyes was plotted graphically for several decades. Whether or not the increase in myopia stopped at the age of 15 was found to depend on habits of reading and near work. In one case the myopia was —6.50 D. at the age of 25 and increased an equal amount each year, to reach —20.00 D. at the age of 82.

Jampolsky and Flom[25] describe the perplexing case of a 25-year-old woman who had attacks lasting about 24 hours in which the lens moved within 0.5 mm. of the cornea and produced —5.00 D. of myopia. The attacks were apparently related to menstrual periods and seemed to regress without complication.

Sato and associates[26] present a series of 32 cases in which radial incisions of the inner half of the cornea decreased the myopia from 1.50 to 7.00 D. without objectionable scar.

NIGHT MYOPIA

Prescription of minus lenses for use at night has not been widely advocated, but it must now be considered. Authorities agree that the dark-adapted eye is from 1.00 to 1.75 D. more myopic than the same eye in daylight. There is controversy about whether the myopia is due to increased accommodative tone or to spherical and chromatic aberration of the human eye with a large pupil. The excellent photographs by Koomen, Scolnik, and Tousey[27] showed no changes in curvature of the front of the lens before and after dark adaptation. Campbell[28] objects that they did not provide a visual fixation target, which is necessary for accommodation. He points out that presbyopes became about 0.75 D. less myopic in the dark than nonpresbyopes. Tousey and associates[29] answered that accommodation does vary according to the stimulus in darkness but that the amount of night myopia can be sufficiently explained by aberration and a large pupil. The pupils of presbyopes do not fully dilate at night; consequently, the aberration is reduced. Otero[30] explains that in young adults with natural surroundings, both accommodation and aberration combine to produce night myopia.

The effect of accommodation to reduce the spherical aberration of the human eye produced by a large pupil is shown by Ivanoff ‡ to be helpful up to 1 or 2 D. More accommodation would produce the opposite type of aberration, in which axial rays would be refracted more than peripheral rays. This conforms to the visual needs in night vision. It may also explain why many young hypermetropes prefer to remain undercorrected by glasses, even in daylight.

BINOCULAR REFRACTION

The advantages of refraction under conditions resembling normal binocular vision are discussed by Wilmut,[33] Cook,[34] and Jäger.[35] There is better relaxation of accommodative tone in most cases, and the fusion lock prevents cyclotorsion of the eye being tested. Possible accommodative efforts due to heterophoria are automatically compensated. Wilmut used a method in which both eyes could fuse all peripheral objects, but the eye not being tested was prevented from seeing the test types by a mirror. He believes that the use of Polaroid separation would be a more convenient procedure, with the same advantages.

‡ References 31 and 32.

ACCOMMODATION

Koch,[36] editor of the *American Journal of Optometry*, states that public health officers, educators, and certain ophthalmological leaders will eventually urge optometrists to use cycloplegics in some refractions, mydriatics in some examinations, and surface anesthetics for tonometry. This use is now routine in some military clinics.

De Ocampo[37] reports 55 cases in which Filipinos had refraction with the use of atropine, followed by diisopropyl fluorophosphate, 0.1% at 30-minute intervals until recovery of accommodation. It should be noted that in this country use of diisopropyl fluorophosphate has been followed by painful spasm and, in a few cases, retinal detachment.

New cycloplegic drugs are described by Gettes and Leopold[38] and by Milder and Riffenburgh.[39] Residual accommodation was measured by test type, the Prince rule, with a +3.00 D. lens before each eye. It was agreed that Cyclogyl, a quick-acting cycloplegic of brief duration, compared well with homatropine if the refraction could be done within 30 minutes of instillation of the first drop. If not, additional drops should be given.

The limits of accommodation and convergence were measured by Monjé[40] from the outer orbital margin with the Landolt ring on a card as the test object. The end-point taken was the disappearance of the gap in the ring as the card was brought in from a distance. The author concludes that asthenopia was more frequently due to weak convergence than to insufficient accommodation. He agrees with Meesmann,[41] that accommodation is subject to antagonistic parasympathetic and sympathetic innervation. Because of the accommodation-convergence reflex, heterophoria is closely related to this innervational tone. Similar conclusions are reached by Siebeck § from tests of the accommodative tone of eyes treated by atropine, physostigmine, and epinephrine.

The concept of antagonistic accommodative innervation has been unpopular because of its use by certain practitioners to explain their treatment of myopia without glasses. Claims of negative accommodation used to be frequent but in recent years have become quite rare. Giglio[44] reports the case of a patient with 8 D. of myopia who at times, with considerable effort, could read 20/25 test type without glasses at 20 ft. (6 meters).

Rasgorshek[45] objects that the usual tests for residual accommodation are inaccurate. He favors the use of Sheard's dynamic retinoscopy. Brickley and Ogle[46] go a step further to show that the usual tests for residual accommodation do not control the effects of ocular depth of focus and the ability to interpret blurred imagery. Their tests of the accommodative level with binocular fixation at various distances under cycloplegia by means of stigmatoscopy in a haploscope showed no accommodation at all. Their apparatus consisted of a head holder from which both eyes could observe a target straight ahead. The eye for which the accommodative level was to be tested was able, by a semitransparent mirror, to observe a point of light which could be moved a distance optically equal to a range of from 25 cm. to infinity. Although for convenience the light was mounted on a side-arm, it appeared superimposed straight ahead and could be moved by the patient until perfectly sharp. Miles[47] used a similar instrument in a study of the ranges of clear

§ References 42 and 43.

vision through trifocal lens powers in presbyopes. His tests of the level of accommodation in vision at various distances showed that clear vision is due mostly to depth of focus and interpretation of blurred imagery. Active accommodation in presbyopia is relatively unimportant. The beneficial results reported by patients wearing trifocals was explained by the dilution of bifocal "jump" and doubling and by elimination of accommodative stimuli.

Brickley and Ogle, Miles, and also Graff [48] found that normal young adults fixing binocularly at infinity did not relax the accommodation beyond a distance of 2 meters. There was also a considerable lag or underaccommodation for distances of fixation nearer than 1 meter. Further studies should be made with other types of apparatus and other sizes and types of test objects.

Many factors, such as sense of nearness, stereoscopic disparity, size of retinal blur circles, and the relatively unstable convergence-accommodation reflex, contribute to the accommodative tone, according to Fincham.[49] He measured accommodative tone with his coincidence optometer on the side-arm of a haploscope while both eyes fixed a target straight ahead. When he stimulated accommodation by interposing minus lenses and then released it by plus lenses, there was no wavering of the accommodation level in any case. It immediately changed in that direction necessary to correct the vergence of rays at the retina. With monochromatic light or in subjects with color blindness, the change in accommodation was frequently slow and uncertain in direction. He therefore concludes that accommodation usually depends on the relation of a color fringe to the main portion of a retinal image.

THE ACCOMMODATION-CONVERGENCE REFLEX

The number of prism diopters of convergence excited by 1 D. of accommodation is characteristic of the individual and is called the accommodation-convergence ratio. It has practical value for refraction, according to many writers. If the ratio is low—1 to 3—the plus power and the amount of the reading addition may be decreased. If the ratio is as high as 5 or 7, the plus power and the amount of reading addition may be increased. Methods of measurement and various characteristics of the ratio are discussed by Asher [50] and Fry.[51]

RETINAL RIVALRY, DOMINANCE, FUSION, AND DEPTH PERCEPTION

Theories of binocular vision are turning again toward the dominance and rivalry ideas of F. H. Verhoeff. That perfect fusion and stereopsis may still leave something to be desired has long been known in the use of stereoscopic range finders and mapping equipment. Hamburger [52] found that the men whose stereopsis was perfect by every known test and who could not perform efficiently the work with precise stereoscopic equipment had high monocular dominance. On rivalry tests, in which the eyes were presented with different images in a stereoscope, the image seen by one eye predominated in consciousness. Alternation was slow or absent. Persons with good stereopsis who were more successful in the use of the stereoscopic equipment showed rapid alternation of the two images in the rivalry tests.

In tests of normal persons with stereoscopic slides of his own design, Asher [53] confirmed the importance of alternation for stereopsis. At any moment, for any pair of corresponding retinal areas, one area alone can be dominant and reach higher levels. An adjacent retinal area may at the same time be recessive. The final image

in consciousness consists of a mosaic of images from the right and left eyes. If one eye has any advantage in brightness or in point of view, its image gains strength. At the same time, in monocular vision any contour or figure will cause suppression of its own background.

A related nonstereoscopic binocular depth effect is termed "anisodominance" by Miles.[54] Persons with high monocular dominance, anisocoria, or an inequality of retinal image brightness in the two eyes make errors in judgment of the relative distance of objects of any shape. If objects of sufficient contrast are equidistant from the eyes, and if they appear brighter to the right eye than to the left, the object to the right will appear nearer. The objects do not have to be identical, but they must have bulk. Since a dominant eye usually sees objects brighter than the recessive eye, a right-eyed person will see the right of two equidistant objects nearer. The anisodominance error is now apparent in the original publication by Howard in his stereopsis test. It explains errors in the use of the Howard-Dolman depth perception apparatus attributed by Scott and Sumner [55] to psychological clues. It also applies to the results published by Sloan and Altman.[56]

Conflicts in the dominance of eye, hand, and brain hemisphere may cause problems in reading.[57,58] Methods of diagnosis and treatment are discussed by Hughes.[57] Cohen [58] affirms the classification of dominance as motor and sensory. Motor dominance has to do with sighting, or eye-directed body movements, while sensory dominance is engaged in fusion or rivalry. Retinal rivalry is a precerebral function, according to Wirth.[59] He found that during retinal rivalry stimulation, the pupil light reflex was stronger in that eye which for the moment was dominant. The relation of motor to sensory dominance was studied by Francis and Harwood.[60]

Winkelman [61] distinguishes between sensory fusion, with its more complex relation to perception, which is cerebral, and motor fusion, which is probably a conditioned reflex. If I understand him correctly, his "momentary primitive fusional movement" is probably due to retinal slip or fixation disparity.

The problem of rivalry and suppression of images seen in physiological diplopia is discussed in Halldén's [62] long paper. The importance in orthoptics of strictly foveal fusion targets for increasing the amplitude in small children is emphasized by Coates.[63] Peripheral targets, he says, produce fixation disparity, which is a handicap to fusion.

THE PULFRICH STEREOEFFECT

A pendulum moving in a frontal plane will appear to describe an ellipse instead of a line if for some reason the image of one retina is brighter than the other. Fischer and Haberich [64] attribute it to a lag in perception in the darker-seeing eye, which would produce an amount of stereoscopic disparity corresponding to the depth of the ellipse and also to the extent of Panum's fusional areas. Trincker [65] points out that for some observers the trajectory of the pendulum took various shapes, according to the mental set.

Miles [66] elaborated upon experiments by A. Ames Jr. to show that the Pulfrich effect could be duplicated without reducing the illumination or changing the adaptation of one eye by means of an afocal magnifier before one eye. That optically induced disparity works as well as perception-time disparity adds weight to the stereoscopic theory. Fischer suggested that since the Pulfrich stereoeffect could be observed only with a moving target, and since the maximum displacement

occurred in the part of the trajectory where the pendular motion was greatest, the Mach-Dvorak phenomenon must be involved. This means that only rapid or jerky movements are effective visual stimuli, as in the case of a bird being stalked by a cat. The same reasoning applies to the Ames size-lens effect.

Siebeck [67] states that patients with anisocoria have a spontaneous Pulfrich stereoeffect and warns of orientation errors in fast city traffic.

SIZE AND DISTANCE PERCEPTION

Size constancy is a phenomenon of vision by which objects appear to be the same size regardless of their distance. The hand is twice as large before the face as it is at arm's length, but the size apparently remains the same. The phenomenon exists as far distant as 300 ft. (9 meters), according to Renshaw.[68] The apparent-size data obtained with his stereodisparator resemble those for the famous "alley experiments." The apparent area of a target can be predicted if the physical size and distance are known. However, the effect of experimental conditions on size perception is very important, and the figures may not apply to certain natural surroundings. Fry [69] relates Renshaw's figures to those of Gilinski and Luneberg. In spite of the imposing title, Boeder [70] has put in simple terms the recent developments in comparing perceived and physical space. Although every person is different in his space perception, the amount of error is constant. Present tests include those for aniseikonia, stereopsis, the horopter, size constancy, and the estimation of distances and angles. The error in space judgment is different in myopes than in hypermetropes. Blank [71] describes the techniques of measurement being developed at the Knapp Laboratory of Physical Optics.

A new method of measuring the subjective horopter which does not require that the subject be trained is presented by Junker.[72] Binocular vision is maintained at one point while a rotating sector disc acts like a cover test on peripherally viewed vertical wires. When the upper and lower halves cease to appear to jump in alternate presentation, the wire target is on the horopter.

Experiments by Howarth [73] showed that while visual acuity decreased with lowered light intensity, the stereopsis increased within certain limits. He attributes the improved depth perception to shorter depth of focus from the enlarged pupil. This judgment of depth from the sharpness of focus of the object fixed as compared with blurred objects at other distances is a monocular clue and should not be related to stereopsis as the term is generally defined.

Krummel [74] used the Monjé three-wire stereoscopic test on 246 young men with normal eyes. The resulting data showed a binomial stereoscopic acuity distribution curve. Ogle [75] measured the precision of stereopsis with gradually increasing disparity. In his subjects there was a decrease in stereopsis related exponentially to increased disparity. The range of disparities within which stereopsis did exist with the proportional changes in stereoscopic acuity suggested to Ogle a neuroanatomic foundation. There could be an intermingling of neural pathways from the two retinas among multiple arborized cortical dendrites.

An article of interest to architects and artists which concerns the esthetics of shape was written by ten Doesschate.[76] He suggests that Greek and Egyptian artists had secrets still unknown to us which may be related to the incongruity of space values of nasal and temporal retinas.

The classical partition experiments were repeated by Brown.[77] He found that the apparent size of objects seen on the upper retina as compared with that of objects seen on the lower varied considerably, but that apparent size on the nasal retina as compared with that on the temporal was stable and repeatable over periods of weeks. His subjects fixed monocularly on the sliding center of a luminous line target. The subject could move the fixation target in either direction until the length on one side of the line appeared equal to that on the other. The horizontal values were considerably different in various subjects, but a wide variant of one eye was usually neutralized by the opposite type of partition in the other. Consequently, the subjects tested all showed bilateral partition corresponding to a normal slightly convex horopter at the 2-meter distance.

The value for depth perception of proprioceptive clues from convergence or innervation for convergence by images in physiological diplopia is discussed by Pacalin[78] and Lyons.[79] The depth perception experiments and demonstrations by A. Ames Jr. have become available in a book by Ittelson.[80]

DEPTH OF FOCUS

It has been mentioned that much of what has been called amplitude of accommodation is ocular depth of focus. If the depth of focus on normal-sized test type with a medium pupil is the reported 0.50 D., Coates[81] declares it nonsense to provide 0.12 D. steps in trial case lenses. Many would be inclined to agree, especially for cases in which the subjective refraction seems to vary from day to day. The matter is too complex for snap judgment. Some patients demand precision to the last 0.12 D., and a comfortable balance of convergence tone in some persons seems to depend on slight difference in sphere. The main point in Coates's paper is that a patient may have two refractive corrections, due to variation in the corneal surface power. A man aged 70 could see equally well with +2.50 or with —6.50 D. at distance. No intermediate power would be accepted.

Westheimer[82] derived formulae for estimation of the range of clear vision through multifocal lenses in various types of ametropia and powers of reading addition. The age of onset of presbyopia varied with racial background, according to Rambo.[83] Women in India may be presbyopic by the age of 37. The Greeks wait until the age of 40 for bifocal glasses, while Scandinavians may continue to have adequate accommodation until the age of 48.

EFFECT OF OCULAR SURGERY ON REFRACTION

In 16 eyes on which he advanced horizontal rectus muscles, Borsello[84] found a permanent increase of astigmatism with the rule up to 1.10 D. Sato[85] reports surgical cures of corneal astigmatism. Pavišić[86] compared the keratometer readings before and after surgery for pterygium in 64 cases. Amsler[87] demonstrated the usefulness of photographs of corneal images of the Placido disk before and after corneal surgery.

ASTIGMATISM

A very important paper was written by Chilaris[88] on the corneal astigmatism of more than 2,800 patients. He found oblique astigmatism to be commoner in myopia, hypotony of the globe, and enophthalmos. Of the normal controls, 11% had no astigmatism, 42% had astigmatism with the rule, and 9% had astigmatism

against the rule. Of the infants, 11% had no astigmatism, 56% had astigmatism with the rule, and 7% had astigmatism against the rule. Of myopes, 11% had no astigmatism, 24% had astigmatism with the rule, and 17% had astigmatism against the rule. Of hypermetropes, 7% had no astigmatism, 39% had astigmatism with the rule, and 10% had astigmatism against the rule. Of patients with exophthalmos, 2% had no astigmatism, 46% had astigmatism with the rule, and 8% astigmatism against the rule. Of patients with enophthalmos, 11% had no astigmatism, 16% had astigmatism with the rule, and 24% had astigmatism against the rule.

From a study of refractive data on 27 identical and 12 fraternal twins, Hofstetter and Rife[89] conclude that astigmatism is acquired, whereas spherical refractive errors are inherited.

ANISOMETROPIA AND ANISEIKONIA

The treatment of hyperphoria in the reading position of gaze induced by correcting lenses for anisometropia has always been a problem. The use of certain base curves and center lens thicknesses (as in aniseikonic size lenses), suggested by Friedenwald nine years ago, has been found to be a practical solution by Lebensohn,[90] especially in patients requiring bifocal glasses.

The problem of monocular aphakia is discussed by Cowan[91] and by Rosenbloom.[92] An excellent review of clinical aniseikonia was written by one of the original Dartmouth group, Bannon.[93]

RELATION OF EYE MOVEMENTS TO VERTIGO

Some patients suffer vertigo when breaking in new glasses or when watching moving scenery or water, but the treatment of labyrinthine vertigo by prisms in spectacles, advised by Baron and Fowler,[94] has not proved successful. Vertigo has not been considered a symptom of heterophoria. Hilding[95] found no evidence of reflex paths relating heterophoria with labyrinthine stimulation. Giorgio and Guilio[96] report changes in accommodative tone upon labyrinthine stimulation of guinea pigs. If the reflex exists, it should be even more easily demonstrated on human beings.

Hauty[97] found that the amplitude of nystagmus after body rotation was directly related to the acceleration. The duration of nystagmus was not affected by acceleration, but depended on the duration of acceleration. An interesting method of producing in a normal person a nystagmus resembling the pendular type in amblyopia is described by ten Doesschate.[98] The subject looks at a point of light through a +40.00 D. lens placed in a trial frame at such a distance that the image focuses on the center of rotation of the eye. Under this condition eye movements do not move the blurred retinal image from a single position.

SUNGLASSES AND GLARE

In recent reviews, Sterling[99] recommends medium green sunglasses for general outdoor use, while Hoffmann[100] prefers a neutral medium tint for better color discrimination. Miles[101] criticizes advertising of tinted lenses alleged to aid night driving by reducing the amount of ultraviolet light striking the retina during the day. The advertising should make clear that tinted lenses should not be worn for night driving. The effect of whatever tinted lens may be used would be negligible

because little or no ultraviolet light can pass normal cornea and lens. The relation of ultraviolet light to human vision is reviewed fully by Ogilvie,[102] and its absorption by ocular media is measured by Weale.[103]

Erythropsia was found by Dubois-Poulsen and Deswartes [104] to be due to an exhaustion of the entire stock of visual purple by excess light. It occurred in eclipse blindness, snow blindness, aphakia, albinism, iris coloboma, and aniridia. An article by Simpson [105] on ocular haloes and coronas may be useful and interesting to those who study glaucoma and the use of contact lenses. An article on the Tyndall phenomenon was written by LaMer and Kerker.[106]

The discomfort and loss of visual acuity from glare was shown by Fry and Alpern ‖ to be due to intraocular stray light, and not to intraretinal reflexes, which reduce foveal sensitivity. Rays from the glare source are reflected time and again from the peripheral retina, from whence they finally strike and reduce the contrast of the foveal image.

COLOR VISION TESTING

The physicist Richter [109] advised wider use of quantitative instruments for color vision testing. The anomaloscope is so sensitive that variations in normal color sense from winter to summer can be demonstrated. Terms like "red-green blindness" are becoming obsolete. The Ishihara and similar tests are qualitative and inconvenient in that they require pure daylight. Schmidt [110] states that artificial daylight of standard color temperature and intensity could be used.

Foveal tritanopia means color blindness to small test patterns as it occurs in normal subjects, according to Burnham and Newhall,[111] and Thomson.[112] That some deuteranopes and protanopes appear to improve in color perception when the test targets are larger in area is reported by Jaeger and Kroker.[113] By relating color discrimination to the stimulation of accommodation, Fincham [114] concludes that color blindness is a retinal, not a cerebral, defect. Hess [115] devised an experiment using the Fechner colors from a rotating black and white cylinder for evidence that color vision is a retinal function.

Amateur color enthusiasts will find "Science of Color," by the Committee on Colorimetry of the Optical Society of America,[116] a treasure. The first two-thirds of the book is a simple account of the history, physics, physiology, and psychology of color. One issue of the *British Medical Bulletin* in 1953 [117] is devoted to the physiology of vision. Seven of the 11 articles are about color.

Weale ¶ continued his research on color discrimination of peripheral retina. In light adaptation, the periphery was more sensitive to yellow and blue than was expected. In two articles, Hurvich and Jameson # call attention to a "shoulder" in the foveal luminosity curves at 400 to 420 μ. Weale [103] suggests that such a "hump" might be due to the overlap of two photomechanisms, or there might be absorption effects by ocular media or retinal pigment. The "hump," or greater sensitivity to blue, is true not only of the macula but also of the periphery at certain levels of adaptation and must be a phenomenon of both rods and cones.

‖ References 107 and 108.

¶ References 118 and 119.

References 120 and 121.

The effect on visual thresholds of monochromatic lights or vision through yellow filters was studied by Schwarz [122] and Kuhl,[123] who found vision improved in yellow or in violet-free light. Hartridge,[124] like some others, disagreed with this conclusion, since lenses correcting ocular chromatic aberration do not improve visual acuity. The resolving power of the eye in white light, he found, was as good as in a theoretically perfect optical instrument. According to the Hartridge theory, color aberration fringes are actively suppressed by the retina.

Motokawa and Ebe * studied color and visual function by means of a unique method involving the changes in threshold to phosphenes excited with an alternating current applied by electrodes on the temple and forehead. The dark-adapted subject was shown a flash of colored light. For several seconds afterward, tests were made of the critical flicker rate determined by the alternating skin current at the lowest voltage which would just produce a phosphene. The results were interpreted to mean specific stimulation of retinal elements sensitive to a certain color. The alternating frequencies at threshold after various monochromatic light stimuli came out in harmonics of seven per second.

FLICKER FUSION FREQUENCY

Continued interest in the use of flicker fusion frequency for clinical perimetry is shown by the work of Henderson [128] and of Rossetti and Santelli.[129] Miles still uses flicker perimetry regularly for detection of early glaucoma and early diseases of the visual pathways.

Brill and associates [130] state that the Krasno-Ivy glyceryl trinitrate (nitroglycerin) flicker test is valuable for prognosis in early toxemia of pregnancy. The onset of toxemia could be predicted before any other clinical sign appeared. For routine office use in the diagnosis of cardiovascular disease, the Krasno-Ivy test has not been entirely dependable. It could be considerably improved by stimulating areas near the blind spots instead of the fovea.

Yonemura [131] found the flicker fusion frequency decreased in patients with reversible nutritional retrobulbar neuritis without other signs of functional loss.

Alpern and Spencer [132] believe that the increase of flicker fusion frequency in peripheral tests as compared with foveal tests is spurious and would not be present if the pupillary size could be controlled. This point is of great theoretical importance. Whether the pupil is large or small, the amount of light striking the peripheral retina in oblique rays is decreased by the elliptical shape of the pupil. In the clinical conditions used by Miles, dilatation of the pupil increases central flicker fusion rates perhaps three flashes per second. Peripheral flicker fusion rates are elevated somewhat more than this after dilatation. Some writers had assumed that alternate firing of groups of rods and cones using the same peripheral ganglion cell accounted for the difference.

Flicker fusion tests are not suitable for estimation of visual fatique according to Ryan [133] and Brozek [134] and their associates and cannot be influenced by illusions of size and brightness (Berger and Mahneke [135]). A monumental series of abstracts on flicker fusion phenomena was prepared by Landis.[136]

* References 125 and 126.

VISUAL FIELDS

The French textbook "Le champ visuel," by Dubois-Poulsen and associates,[137] does for visual fields what Polyak's book did for the retina. Dubois-Poulsen has emphasized the relative sensitivity of parts of a visual field, not the particular shape of a contour. He [138] made the point that vision of one area of a visual field should be compared with that of a paired area on the other side of the central vertical line. The interpretation of visual fields taken for neurological conditions should resemble such tests as comparison of the strength of the knee jerks and the Bender [139] bilateral touch tests. This concept has grown partly by experience in the use of flicker fusion fields, which by its method of recording suggests relative sensitivity, and not contour.

Daenen [140] suggests the use of contact lenses to obtain comparable fields in high myopia and aphakia. Havener and McReynolds [141] urge the use of correcting glasses in high ametropia for visual fields. The Traquair island is well illustrated by Harms.[142] Scotopic, ultraviolet fluorescence, and other new visual field techniques are described.† Arakawa [147] used Motokawa's phosphene thresholds [125] to take visual fields objectively in animals.

Sédan and Sédan-Bauby [148] determined the effect on angioscotomas of fatique, epinephrine, ephedrine, ergotamine, acetylcholine, atropine, amyl nitrite, alcohol, and tobacco. Aulhorn and Voges [149] showed the differences in visual field isopters taken with a small parallel line target presented with the lines vertical, horizontal, or oblique. The isopter shape appeared as an ellipse in the same direction as the presentation of the target lines. Zanen [150] found a field defect to blue targets characteristic of chorioretinitis. Nerve conduction diseases caused field defects to yellow, white, and red targets.

VISUAL ACUITY

Matters pertaining to visual acuity without glasses are discussed by Benton,[151] Robinson,[152] Fry,[153] and Pascal.[154] Many visual screening devices today use patterns for which the direction of a contour at 45-degree intervals is to be determined. Leibowitz [155] discusses the fact that acuity is greater for erect than for oblique contours and attributes it to the mosaic pattern of rods and cones. One should note the related work by Harrison [156] and Ludvigh.[157] Gilbert [158] defines visual acuity in terms of the broken-ring test object and the "forced-choice" statistical method. Practical matters of target design are discussed by Chapanis,[159] Smeed,[160] and Gerathewohl.[161] Tests of visual acuity by opticokinetic nystagmus on a revolving drum are described by Nicolai [162] and Mackensen.[163]

Papers concerning the determination of visual acuity for clinical purposes are presented by Ehlers,[165] Law,[166] Fink,[167] Maxwell,[168] and Kestenbaum.[169] Their point of view on chart design is practical. Ehlers states the general feeling that sizes of test types selected should be such that a patient can read all but one or two letters in a line and will miss most of those in the next. The differences in size of test type in adjacent lines need not be in geometric or logarithmic progression. Kestenbaum says that records of visual acuity should include the distance of the test. Near vision might be superior to far vision in patients with peripheral lens

† References 143 through 146.

or corneal opacities or with uncorrected astigmatism. Far vision might be better than near vision in the presence of central lens or corneal opacities or of partial macular scotomas.

Cuendet [170] upholds the strict design of visual test charts to conform to Fechner's law that sensation is proportional to the logarithm of the excitation. Ogle [171] points out that charts designed by Snellen, Javal, Green, and the armed forces satisfy the requirements of Fechner's law but that five others which are in common use do not. Ogle expresses the opinion of the Committee of the International Council of Ophthalmology that a decimal system of recording visual acuity is unsatisfactory because it can give no indication of the distance used and implies percentage visual loss. The adoption of the visual angle of resolution in minutes of arc of component parts of test letters is advised for an international standard. The particular geometric progression in size of test types should be determined by the need, not by international standard.

VISUAL FATIQUE AND DISABILITY

Problems related to difficulties in reading are discussed by Orbach,[172] Eames,[173] Neely,[174] Berger,[175] Aulhorn,[176] Park,[177] Kephart,[178] Olson and associates,[179] and Lyle.[180] A handbook on lighting is published by the Illuminating Engineering Society.[181] Weston [182] believes visual fatique to be considerably influenced by fatigue of eye, face, and neck muscles. Riffenburgh [183] found refractive or motility errors not as important in causing symptoms in radar operators as the duration of observation duty or the method used to search the radar screen. The operators should rest after each half-hour, and the eyes should be kept in motion over the screen, with an occasional glance away.

An interesting error of airplane pilots, which probably also occurs on straight, level highways, was described by Clark [184] as "fascination." During monotonous routine flying the eyes develop a hypnotic stare or fixation. Pilots recognize the symptoms but need training in methods to snap out of it. The treatment is to keep the eyes moving.

Retinal adaptation, sometimes termed fatigue, in which an object fixed will periodically disappear and return, was studied by Monjé,[185] Riggs,[186] and Craig,[187] and their associates. In the peripheral retina, the stimulation of areas on an oblique meridian disappears for periods twice as long as similar stimulation on a vertical or horizontal meridian.

DARK ADAPTATION

A new self-recording adaptometer is described by Weidmann. [188] W. Miles [189] discusses adaptometer instrument targets and their use in testing night vision. Peskin [190] found no difference due to race in the dark-adaptation curves of 170 white and 80 Negro subjects, although there were differences corresponding to age and occupation groups. More theoretical problems of night vision were studied by Adair,[191] Brown,[192] Bridgman,[193] and Rushton.[194]

The practical question as to the best method of inducing and maintaining dark adaptation is discussed by W. Miles [195] and by Smith and Dimmick.[196] It is interesting that dark adaptation proceeds almost as rapidly when some vision is permitted through red glasses as it does in complete darkness.

VISUAL PHYSIOLOGY

Knowledge about visual physiology is well summarized in a book by Piéron.[197] He discusses flicker fusion, dark adaptation, glare, the trichromatic theory of color vision, brightness, color blindness, cortical visual mechanisms, and other topics of interest. In his opinion, except for adaptation, vision is more electrical than it is photochemical. Two valuable source books on human vision appeared this year, one by Berens and Sheppard,[198] the other by Weiner and associates.[199]

The Stiles-Crawford directional sensitivity of the retinal receptors is described by Alpern and Benson [200] and Beck [201] as a mechanism to reduce the effect of spherical and chromatic aberration in the human eye. Ten Doesschate [202] devised a method of entoptic imagery of the foveal nerve fiber layer.

THE ELECTRORETINOGRAM AND PHOTIC DRIVING

The literature on electroretinography prior to 1952 is reviewed by Bounds.[203] The subject is also well covered in a book edited by Streiff.[204] Zetterström [205] found the electroretinogram absent in 30 premature and in normal infants at birth. The wave amplitude gradually developed in infants, until at the age of 6 months it became 0.25 mv., as compared with 0.35 mv. in the normal adult. Development of wave amplitude in the premature infant was delayed.

Clinical electroretinography is reported on by Straub,[206] Müller-Limmroth,[207] Henkes,[208] Burian,[209] and Jacobson and O'Brien.[210] Physiological studies are published by Enroth,[211] Best,[212] Kuffler,[213] Rushton,[214] Henkes and Rottier,[215] Armington,[216] and Granit and Wirth.[217]

When the retina is stimulated by a bright light flashing at a rate about 12 per second, or a rate equal to the individual alpha rhythm, the occipital electroencephalographic leads show spikes corresponding to the flash rate. In certain persons, children, and patients with epilepsy, nearly any flashing frequency will drive through and appear on the electroencephalograph record. When the flashing frequency reinforces the alpha rhythm, the natural electrical pulse of the brain, the photic driving, becomes more definite. The flashing frequency may be a harmonic, or a rate twice or three times the alpha rhythm.

In certain persons the bright flashing light will cause "flicker sickness," as described by Ulett.[218] An attack of epilepsy may occur in susceptible patients.

The time of transmission of the retinal response to the cortex can be measured readily by the method of Monnier and von Berger.[219] This time amounts to about 5 msec., and may be decreased in certain diseases of the visual pathways. Clinical studies on transmission time were made by Müller-Limmroth.[220] Photic driving was attempted by Parsons-Smith ‡ in a group of children with amblyopia ex anopsia. All the children had had orthoptic training. Those with amblyopia ex anopsia did show more electroencephalographic abnormalities. There was no difference noted in regard to photic driving. Motokawa [223] used various colors of light for photic driving. He found no pattern or amplitude differences for equal physical amounts of light.

‡ References 221 and 222.

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Burton Chance, M.D., *Chairman pro tem*

M. Luther Kauffman, M.D., *Clerk*

Dec. 17, 1953

Malignant Glaucoma. Dr. P. Robb McDonald.

A 50-year-old white man was admitted to the Wills Eye Hospital with a diagnosis of narrow-angle glaucoma of the right eye of 10 months' duration. The tension had been adequately controlled until a few days before admission. The diagnosis had been made on routine examination, and there was no history of an acute attack. The vision with correction was 6/9 in both eyes. Gonioscopy revealed a narrow angle in both eyes and numerous anterior synechiae in the right eye. The tension in the right eye could not be reduced below 30 mm. Hg (Schiøtz).

An iridencleisis was performed on the right eye, and the following day acute glaucoma developed in the left eye. This was not controlled with miotics; so a peripheral basal iridectomy was performed. The postoperative course was stormy in both eyes, with tension ranging from 26 to 63 mm. Hg (Schiøtz). An intracapsular cataract extraction, without loss of vitreous, was performed on the right eye. The chamber remained shallow, but the tension was controlled. The left eye remained fairly well controlled for a time, and then cyclodialysis was performed.

The cyclodialysis functioned temporarily and was followed by an Elliot trephine operation, with control of the tension for four months. The lens in the left eye was finally removed intracapsularly, again without loss of vitreous. The postoperative course in this eye was uneventful. The chamber has remained of moderate depth, and the corrected vision is 6/60. The vision in the right eye has been maintained at 6/12 with correction.

The tension in both eyes has remained within low normal limits for six months.

The management of malignant glaucoma was discussed.

DISCUSSION

Dr. I. S. Tassman: The emotional state of the patient can be an important factor in the occurrence of glaucoma in the second eye. It was indicated in the paper that this patient was emotionally disturbed. I have seen cases in which operation was performed for glaucoma in the one eye and an acute attack developed in the second eye before discharge from the hospital. In another instance, the patient suffered an acute attack of glaucoma in one eye while still hospitalized after removal of the gall bladder. The worry, concern, and disturbed emotional state in connection with the first operation was a prominent manifestation here also.

Dr. P. Robb McDonald: This patient was not very emotional until the day after operation, when I took the bandages off, and he suddenly realized he could not see a thing out of either eye. He said, "Doc, what's the matter with my good eye?" I think anyone would be rather upset. The only reason he refused miotics at various times was that they caused him severe pain, and we switched from pilocarpine to neostigmine. I think the only drug we did not use was diisopropyl fluorophosphate. This case had a very characteristic course. There are many cases of glaucoma in which the patient has not done well after operation, but this one was obviously of the malignant type, and the condition was not cured until the lenses were removed. I think I could have saved the patient quite a bit of anguish, and myself probably a little, if, 48 hours after the tension went up in the left eye, I had been bold enough to go in and take the lenses out. I have had four or five such cases now; fortunately, they all started with somebody else. It is sometimes a little easier to handle a case that someone else is having trouble with than one of your own.

Surgical Management of Intermittent Exotropia. Dr. Robert D. Mulberger.

The author reviewed the nomenclature, etiology, and methods of examination as they applied to the surgical treatment of intermittent exotropia.

A series of 24 cases which were treated surgically was reported. Twenty of the 24 patients had a bilateral recession of the external rectus muscle to the equator. In 92% of all cases the condition was improved by the surgery.

The author advocated bilateral external rectus recession to the equator in most cases of intermittent exotropia.

DISCUSSION

Dr. William E. Krewson III: Intermittent exotropia is an entity which is encountered much more frequently than is generally realized, as intimated by Dr. Mulberger. Its great frequency is unrecognized because these patients have a manifest exotropia at times and exophoria at others, and the condition changes rapidly from one phase to the other. This intermittent type of exotropia is actually the so-called divergence excess, although many other terms have been used in its description. It is characterized by the following findings: marked exophoria for distance, which on occasions becomes exotropia; excessive prism divergence (overcoming base in prisms); normal prism convergence; normal muscle balance for the near point; normal convergence at the near point; normal rotations, and diplopia, when present, comitant both to the right and to the left. Moreover, these patients seldom have amblyopia, the vision usually being equal in the two eyes. Alternation is not uncommon. After divergence, diplopia may be encountered, and then foveal suppression develops as the case progresses; later even peripheral fusion may be lost. It is sometimes possible to demonstrate normal retinal correspondence when the eyes are in alignment for near, and abnormal retinal correspondence when the eyes are divergent for distance. Secondary convergence insufficiency, that is, divergence for the near point, apparently occurs in about one-fourth of the cases especially as the presbyopic age is approached. Such changes not infrequently are the final stage in the evolution of well-established, or constant, alternating exotropia.

Dr. Mulberger is to be congratulated on the excellent results he has obtained in his series of cases. He has applied the procedure, probably believed by the majority of writers to be the most efficacious, namely, bilateral recession of the lateral rectus muscle. Except in the five clinic cases he mentioned, the same surgical procedure was performed regardless of the amount of divergence deviation. I agree that no one operation will give a fixed amount of correction. In my experience, however, although I have no statistics at this time, larger deviations, especially in well-established cases, must have the bilateral recession of the lateral rectus supplemented by a resection of one or both medial rectus muscles as well. Moreover, when secondary convergence insufficiency occurs, the patient, although still an alternator, tends to fix with one eye, and in these cases probably a recession of the lateral rectus and a resection of the medial rectus of the deviating eye is the first step. Not infrequently additional surgery on the remaining eye is required, and even then the deviation is sometimes difficult to correct. Apparently, Dr. Mulberger's series did not include any such cases, since all his patients were under the presbyopic age, although it may be encountered at any time in life. Vertical deviations, when encountered, are often more marked for distance than for near in cases of intermittent exotropia. It is generally supposed that these are functional and secondary to suppression. If they are greater than 2 D., however, I believe their correction is definitely indicated.

Orthoptics was not included by Dr. Mulberger in the treatment of his cases, and his results justify this elimination. All too often, however, suppression is deeper than is appreciated, and its preoperative removal is certainly an advantage. From a practical standpoint, of course, orthoptic training can be effective only in early cases, and in those of small deviations. Postoperative improvement of amplitude is very helpful, however, if it can be obtained. In the majority of cases, surgery, as

Dr. Mulberger has pointed out, is the method of choice. It is especially effective when applied to the very young child, who has not yet developed the patterns of foveal suppression and who is too young for orthoptic evaluation and treatment.

Experimental Intraocular Infection with Mumps Virus. Dr. H. P. Kirber and Dr. Marie W. Kirber.

This paper is published in this issue of the Archives, page 832.

DISCUSSION

Dr. Werner Henle: As a virologist, I shall stay clear of the ophthalmological problems and, rather, confine my remarks to the virus part. Virus infections of the eye are still a relatively uncharted field, at least from the virologist's point of view. The paper presented by the Kirbers forms an excellent example of what can be done if two specialists, the ophthalmologist and the virologist, get together and work out problems.

This paper has brought into focus several interesting points and problems which have been considered for some time in relation to mumps and to other virus infections. One of the problems concerns the pathogenesis of mumps. We have talked in the past rather readily of "complications" of mumps, such as meningoencephalitis, orchitis, and certain ocular lesions. Actually, we know now that the so-called complications very frequently are part of the primary picture, if not on occasion the only sign of infection with mumps virus. That certainly has been proved for meningoencephalitis, and to some extent also for orchitis, since in such cases mumps virus has been isolated from the spinal fluid and testicular aspirations, respectively. More convincingly, it has been demonstrated experimentally by Coons and his co-workers at Harvard, who traced the spread of virus after infection of monkeys by means of labeled antibodies. They found that the virus was seeded in three to four days throughout the animal, long before the development of clinical signs of disease. It was found not only in the salivary glands but also in the meninges and the central nervous system. We feel, therefore, that mumps virus is seeded very early, and that it becomes a matter of some unknown stimulus to determine in which organ(s) lesions will develop. It is obvious that mumps meningoencephalitis in the absence of salivary gland involvement presents a condition which can be diagnosed properly only by applying specific serologic tests. This suggests that in cases of iritis or iridocyclitis mumps virus may be involved, even if there is no accompanying parotitis, and appropriate serologic tests should be performed.

Another point concerns the question of what is going on in the guinea pig eye. It has been shown that only fully infectious virus produces the lesions. When the virus is inactivated by heat or ultraviolet light, nothing happens. It has also been shown that only active infectious virus injected intraocularly will bring forth a significant antibody response comparable to that seen in human infections, but that if inactivated virus is injected, there is little or no antibody response. Thus, the antibody response cannot be due alone to the antigen injected, and the results would indicate that there was some increase in antigen (virus), and with it a greater antibody response. At least this is the way I should interpret the data. On the other hand, a search for active virus in the eye showed, rather, a decrease from the time of injection over the experimental period. There was no definite evidence then that the virus had multiplied. However, this may be due to the fact that the infectivity titrations are not very sensitive, particularly in view of the relatively large amounts of virus initially injected into the eye. Thus, a slight increase in virus might not be detectable with the technique available.

Yet there are other possibilities to be considered in explaining these observations. It might be that the cells available to the virus in the eye are incapable of supporting a full cycle of propagation; i. e., the cells might not be able to produce fully infectious virus and only an incomplete cycle of propagation may occur. In other words, some virus material is produced, but it never acquires the infectious property and therefore it might not be detected. This is not mere speculation, for such phenomena

have been observed with other viruses. For instance, if influenza virus is injected into the central nervous system of mice, there is no production of infectious virus. We cannot measure an increase in infectious virus; yet we can detect an increase in certain virus properties, as determined by laboratory tests, such as complement fixation and hemagglutination. Apparently, an incomplete cycle of propagation takes place, and no fully infectious virus is produced. The injection of influenza virus into the central nervous system, nevertheless, produces lesions, which frequently lead to convulsions and the death of the animal. It is possible, then, that a reaction of this nature occurs in the guinea pig eye. These are problems which certainly would deserve further consideration and study.

Correspondence

GESELL INSTITUTE ARTICLES

To the Editor:—Among the articles appearing in a syndicated newspaper column entitled "Child Behavior" and coming from the Gesell Institute of Child Development, is a series regarding the treatment of myopia by exercises. It might seem obvious that the published articles do not represent the views of the Department of Ophthalmology of the Yale University School of Medicine, but, since the Gesell Institute is located in New Haven, Conn., we have been receiving from colleagues, even within the State of Connecticut, queries as to why we permitted such articles to come out of Yale University. We wish to call attention to the fact that the Gesell Institute is a private organization, with no connection with Yale University, and that the Yale University School of Medicine has no control over, and does not necessarily sanction, any article coming from this Institute.

R. M. Fasanella, M.D., and Staff
Section of Ophthalmology
Yale University School of Medicine

TESTOSTERONE IN DIABETIC RETINOPATHY

To the Editor:—In the February 1954 issue of the Archives (page 282), in a communication by Dr. Samuel Waldman and myself, there appeared a statement attributed to Dr. Henry Dolger to the effect that he had found testosterone to be of value in 40% of his patients with diabetic retinopathy. It now appears that we have misinterpreted his statement, which was made verbally. Successful results were not obtained in his practice.

We sincerely regret that Dr. Dolger's statement was misinterpreted and wish to publish this retraction.

Louis Pelner, M.D.
1352 Carroll St., Brooklyn 13.

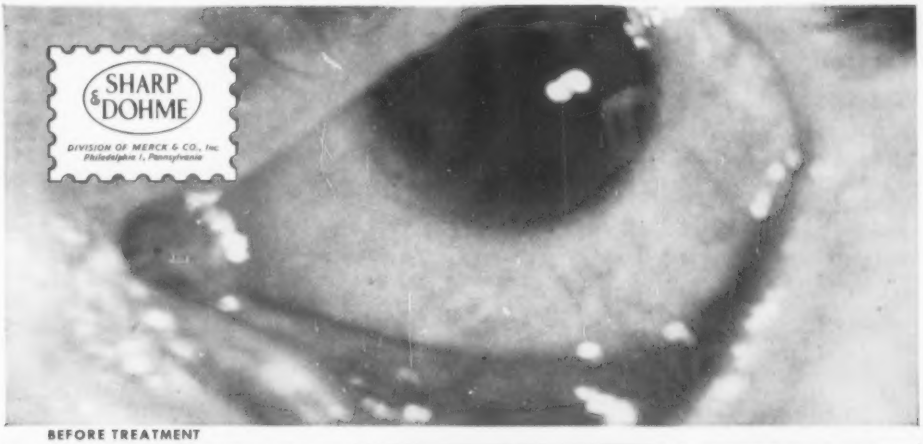
News and Comment

GENERAL NEWS

New Orleans Academy of Ophthalmology.—The subject of the New Orleans Academy of Ophthalmology symposium, to be held in New Orleans, Jan. 31 to Feb. 4, 1955, will be Ocular Motility. A complete program, including names of the guest speakers, will appear in a later issue of the Archives.

PERSONAL NEWS

Dr. Milton Berliner Elected Honorary Member of Greek Society of Ophthalmology.—At the December, 1953, meeting of the Greek Society of Ophthalmology, Dr. Milton Berliner was elected honorary member as an indication of the appreciation of the Society for his contributions to ophthalmology.



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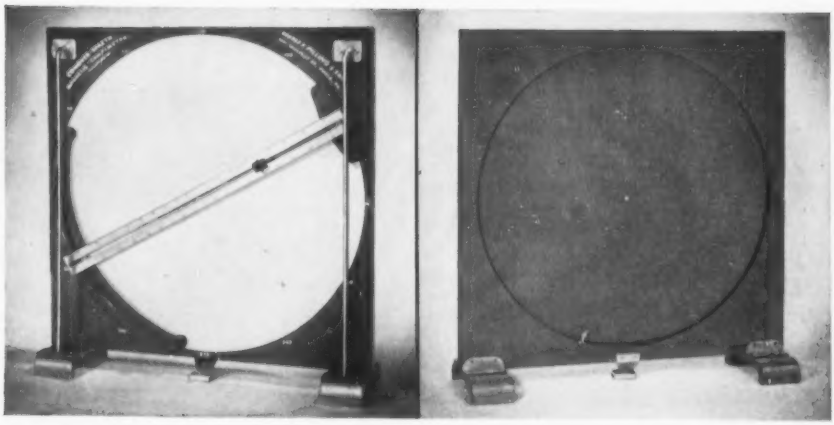

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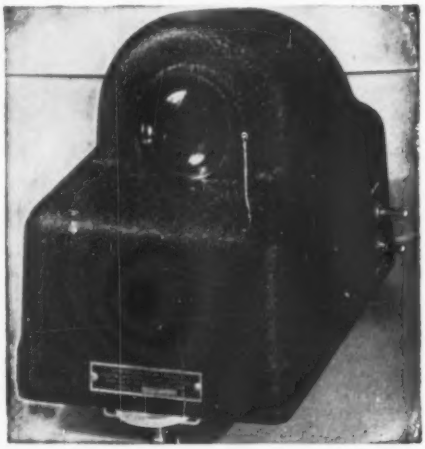

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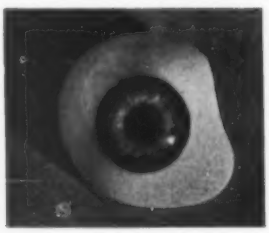

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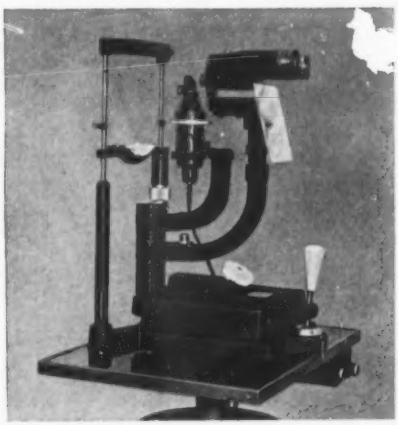

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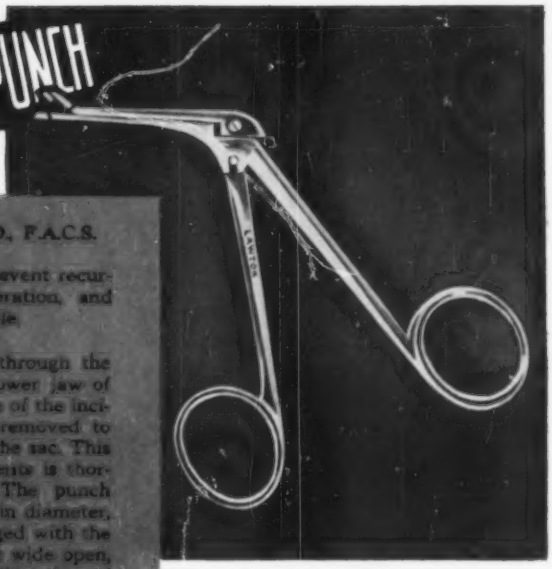

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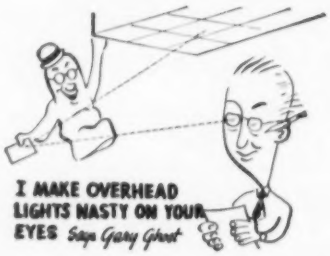

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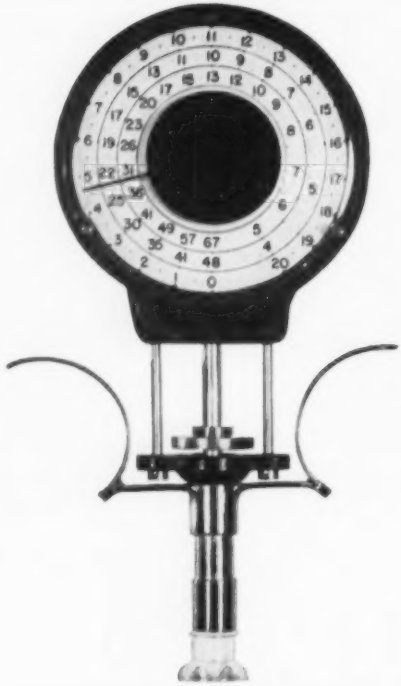

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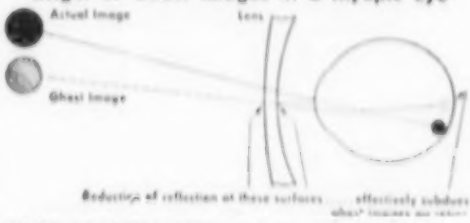

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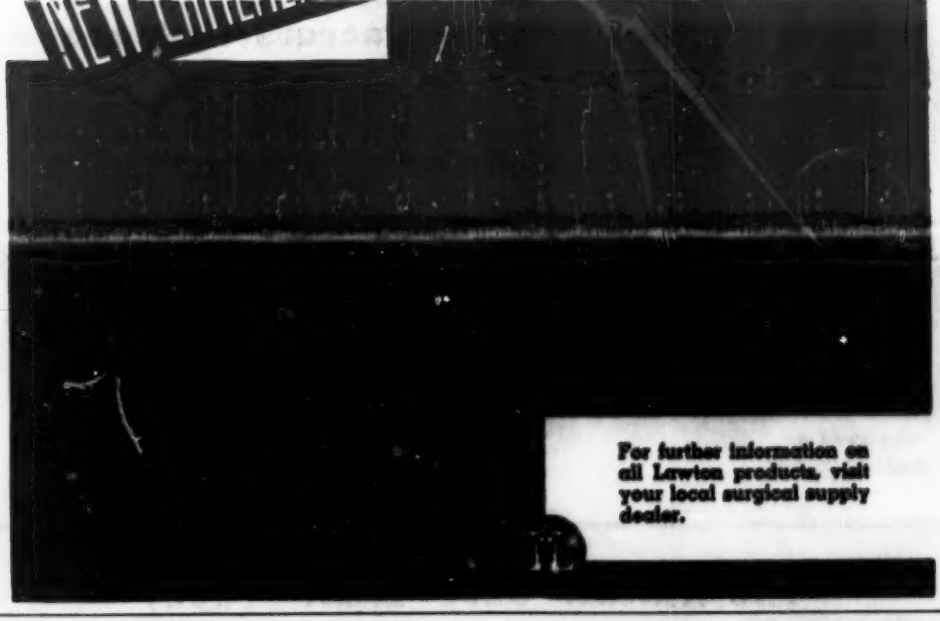

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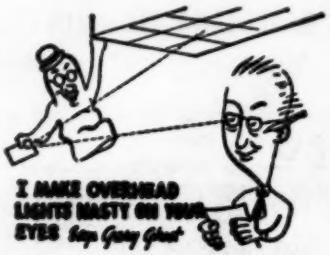

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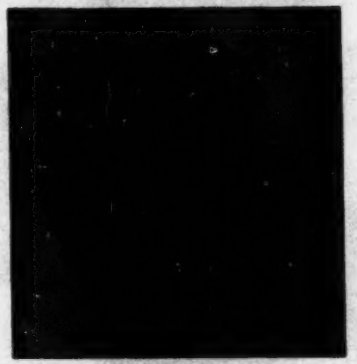

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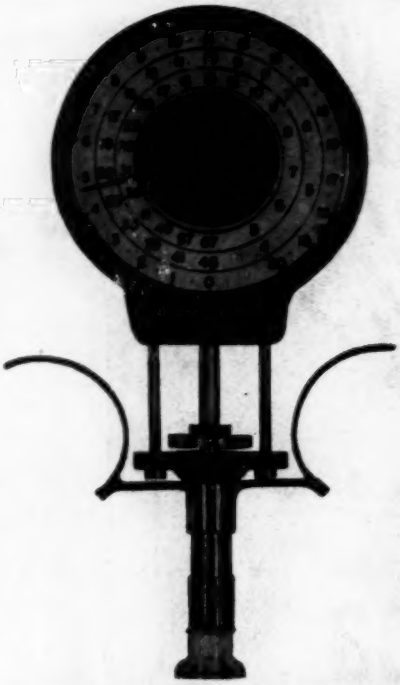

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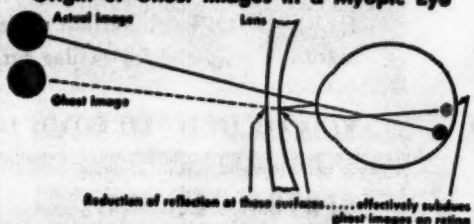

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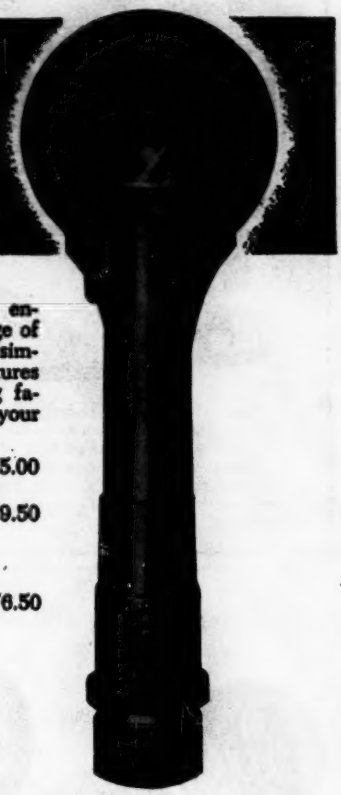

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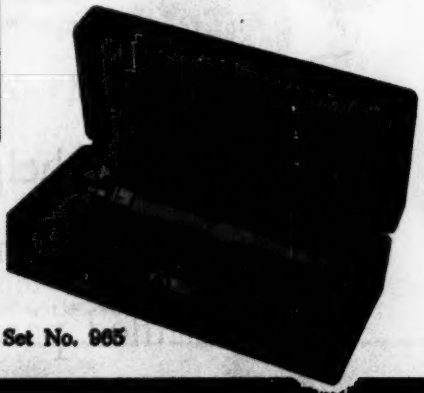

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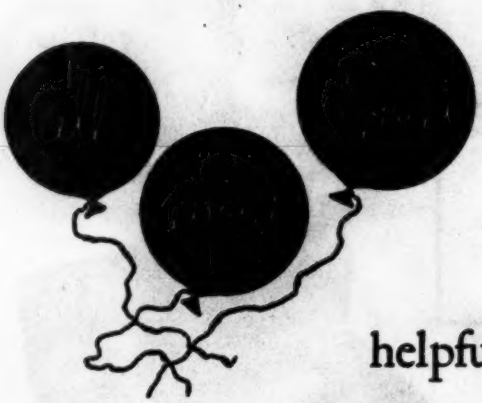

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